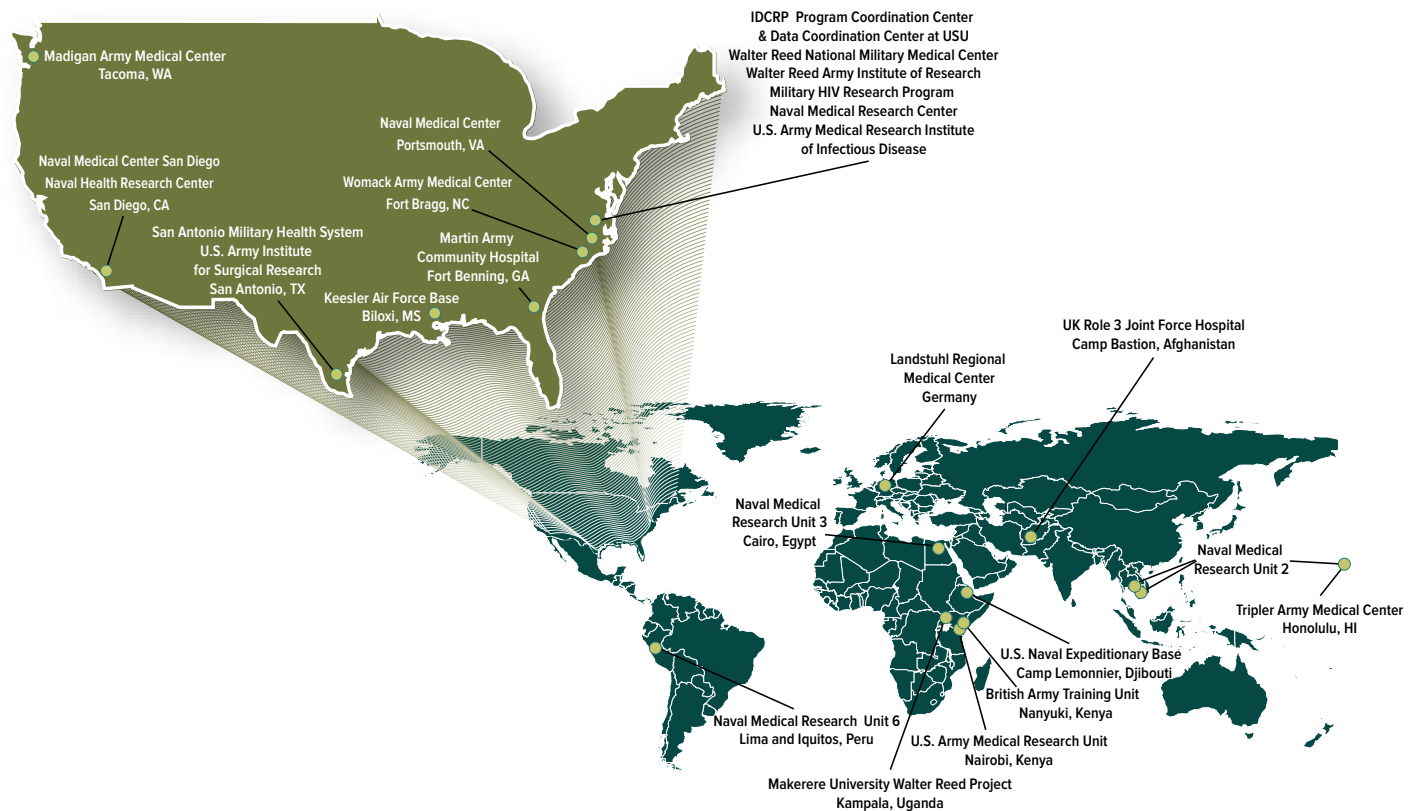


IDCRP

Annual Report 2012
Infectious Disease Clinical Research Program



A Collaboration Between Uniformed Services University & the National Institute of Allergy and Infectious Diseases



Headquartered within the Department of Preventive Medicine and Biometrics at the Uniformed Services University (USU) in Bethesda, MD, the Infectious Disease Clinical Research Program (IDCRP) is a worldwide network of Department of Defense (DoD) clinical and research centers that have collaborated to investigate infectious disease challenges facing the military. With a presence at the largest DoD medical centers, the IDCRP conducts research at 18 military medical facilities and collaborates with 12 military research sites across the world. Working in tandem with active duty investigators at each of these sites, the IDCRP has over 100 employees. Participating centers are partners in the IDCRP's network Infectious Disease Institutional Review Board (IRB) at USU. With a central Scientific and IRB review process, the IDCRP is ideally positioned to conduct multi-center research protocols. At present, there are over 40 active protocols in the IDCRP's research portfolio.

Table of Contents:

Letter from the Program Director	2
Structure	4
Clinical Research Sites	6
Research Focus Areas	12
Trauma/Combat Related Infections	13
Acute Respiratory Infections	16
Operational Deployment/Travel-Associated Infections	18
Biodefense/Emerging Infectious Diseases	20
Skin and Soft Tissue Infections	22
Human Immunodeficiency Virus (HIV)	24
Sexually Transmitted Infections	32
Scientific Support	34
Regulatory Affairs	36
Education	38
Protocols by Focus Area	40
Finances	44
Publications and Presentations	46
Investigator Professional Activities	53
IDCRP at a Glance	Back Cover

Letter from the Program Director

It is hard for me to believe that I've recently completed my third year with the IDCRC and my second year as the Director. I am pleased to say that this year I feel we moved from being a start-up organization to one firing on all cylinders. You will find more details contained in this report, but I thought it worth mentioning some of the highlights of this past year.

- Our HIV work continues to be very productive, with the HIV Natural History Study as the central engine. The numerous publications related to HIV this year included: factors in spontaneous virologic control, HLA mapping and durable host viral control, syphilis incidence, MRSA colonization, chronic kidney disease, and hepatitis B vaccine response and risk of clinical AIDS. We are particularly grateful to the National Institute of Allergy and Infectious Diseases (NIAID) for providing \$7.1 million specifically earmarked to support HIV research over the next three years on top of the core funding already provided through the Interagency Agreement with USU.
- The Trauma Infectious Disease Outcomes Study really took off this year, with new collaborators in the surgical and pathology communities and ongoing work on invasive fungal infections (IFI). The work has become central for clinical practice guidance on IFI and the initial paper describing these novel infections was recently published in *Clinical Infectious Diseases*. In addition, we were very successful in garnering additional funding from the Navy Bureau of Medicine and Surgery (BUMED) as well as starting to build funding from alternate sources to sustain this effort in the coming years.
- The work of the Acute Respiratory Infection Consortium (ARIC) was represented in oral and poster presentations at the 2012 Annual Meeting of the Infectious Disease Society of America in San Diego. We also launched a study at Naval Medical Center San Diego and Brooke Army Medical Center assessing individual versus healthcare provider administration of live attenuated influenza vaccine (FluMist®) with support provided by the Military Vaccine Agency (MILVAX).
- Our study of deployment and travel-associated infectious risk assessment and outcomes in Department of Defense beneficiaries (TravMil) has reached enrollment of >1000 individuals. Our study assessing single dose therapy for acute watery diarrhea and dysentery, occurring in partnership with the UK military in Afghanistan, Kenya, and Djibouti, began in the fall.
- We have a growing effort in the Sexually Transmitted Infections (STI) Focus Area in partnership with the Armed Forces Health Surveillance Center (AFHSC), as we begin a multi-site study on gonococcal resistance and a serosurvey of herpes simplex virus, human papilloma virus, and syphilis amongst active duty military.
- We were very successful in diversifying support for ongoing work on Skin and Soft Tissue Infections (SSTI) with funding coming from the Defense Medical Research and Development Program (DMRDP)



COL Mark Kortepeter, MC, USA
Director, Infectious Disease Clinical
Research Program

and USU. Analysis of data is ongoing from the Centers for Disease Control and Prevention (CDC)-funded study assessing the epidemiology and preventive measures for SSTI among trainees at Fort Benning, GA.

As further evidence of our success, this year we had 29 scientific publications and 26 abstracts accepted to three major infectious disease meetings. In addition, TravMil investigators held a symposium at the 2012 Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) in Atlanta, GA. The symposium, entitled ‘TravMil: Advances in Pre- and Post-Travel Infectious Disease Risk Management Systems’, provided an overview of the study methodology as well as a progress report of the study to-date, including demographic descriptions of the current study population, summaries of travel destinations and risk levels, and descriptive analysis of disease outcomes. Two presentations related to traveler’s diarrhea detailed new diagnostic methods to determine the etiology of illness, as well as rates of utilization, compliance and effectiveness of self-treatment. The final talk of the symposium discussed destination-specific prescription patterns for anti-malarial prophylaxis and factors that affected rates of adherence.

We continued to adapt to the environment as it changed over the past year. We had outgrown our space at USU and with ongoing parking challenges on campus, we moved the majority of our Program Coordination Center (PCC) personnel to a new location on Rockville Pike, a few minutes north of the Bethesda campus. This now brings our PCC personnel together in the same building as our Data Coordination Center, which improves our necessary ongoing dialogue between the scientific and the data managers. We maintain a smaller footprint on campus in Building 28 as our headquarters that allows us to keep close ties with the University as well as the Walter Reed National Military Medical Center (WRNMMC) team.

We had some transition of leadership over the past year as my deputy, Captain Timothy Burgess, was selected as the new Chief of the Infectious Disease Service at WRNMMC. Tim has provided great leadership to the program, both scientifically and operationally. Although we are sorry to see him transition, he will continue to serve as a key advisor, and we are pleased he will remain the Principal Investigator on some of our studies as well as serve as a critical linchpin for IDCRC in this key research site. Dr. Martin Ottolini, our Director of Education, has also moved to a new position in charge of establishing the Capstone research program for medical students at USU. Marty will also maintain ties with us in this role, as well as continuing to run a course on clinical research, serve on the ARIC team and the teaching program for the Armed Forces Infectious Disease Society meetings that IDCRC helps sponsor. We are currently assessing candidates for these key roles. On a more positive note, we were pleased to welcome Gerard Adore as Chief of Operations/Finance and Ed Parmelee as Chief of Data Management.

We continue to be successful in diversifying our funding streams from supporters such as BUMED, the AFHSC, MILVAX, and the DMRDP, and in projecting forward our funding needs over time. We also appreciate the strong, ongoing support from the NIAID, USU, and the Henry M. Jackson Foundation for the Advancement of Military Medicine.

I continue to feel very privileged to serve as the champion of this great network of scientists, clinicians, site managers, clinical research coordinators, regulatory specialists, data managers, biostatisticians, laboratory technicians, and operations managers who are dedicated to our mission of reducing the impact of infectious diseases on the military population. I also appreciate the ongoing support we receive from our active duty infectious disease chiefs and colleagues at the individual research sites, as well as for the members of our Steering Committee, who provide us with regular counsel.

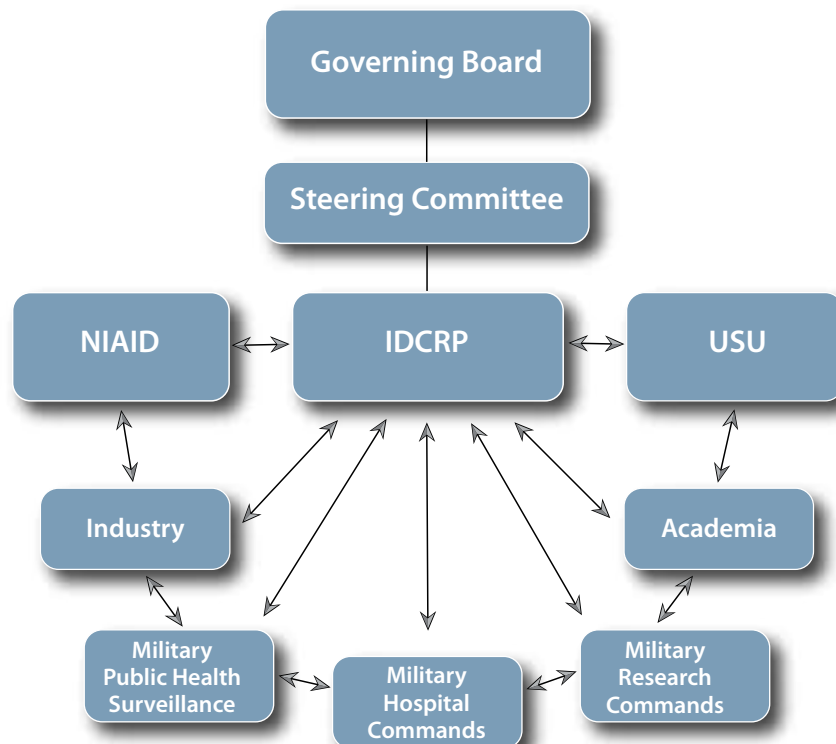


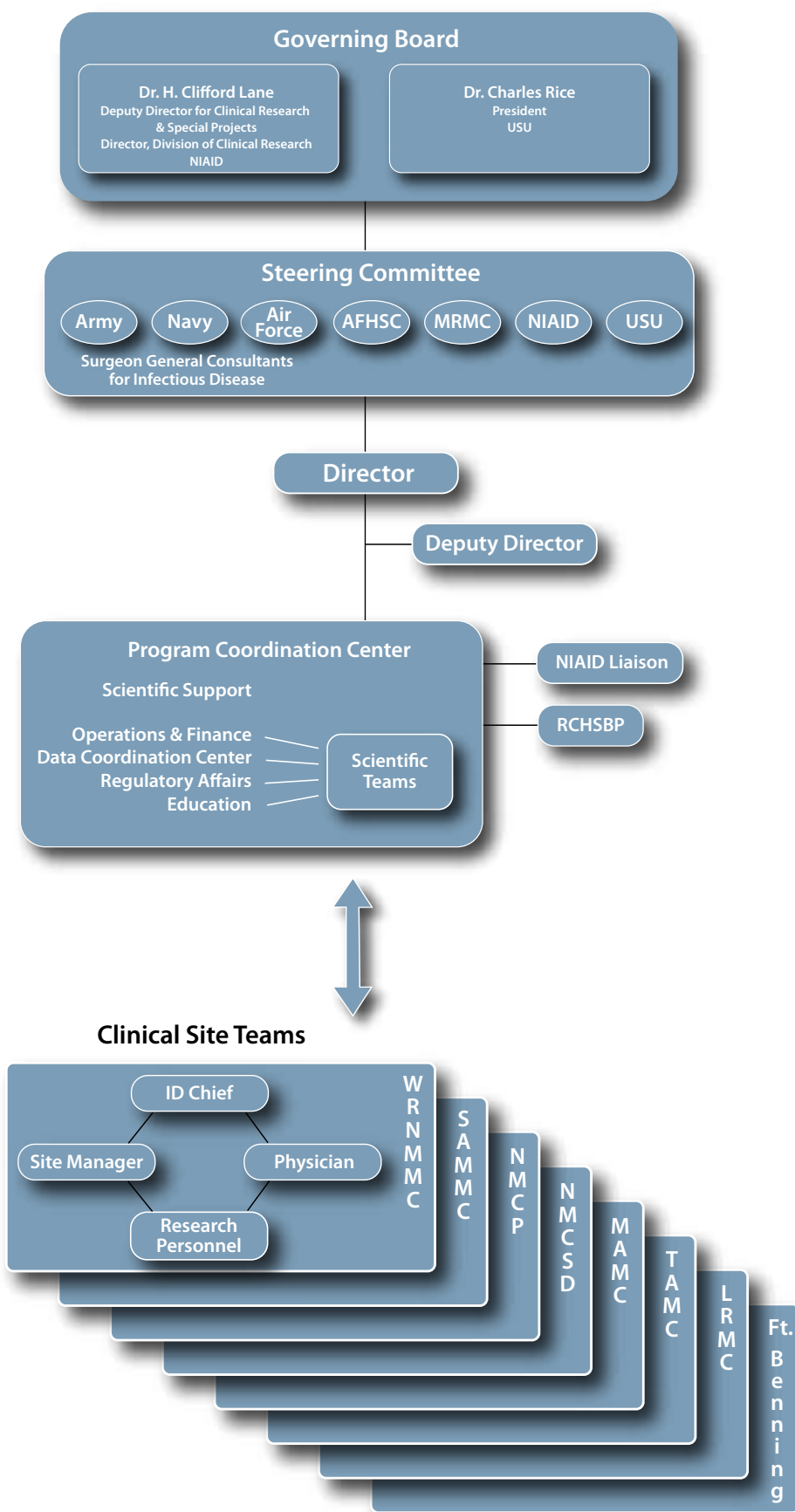
As shown in the figure on the opposite page, the IDCRP Director answers to a Steering Committee made up of seven individuals, including: the Infectious Disease Consultants to the Surgeons General of the Army, Air Force, and Navy, and representatives from the NIAID, Medical Research and Materiel Command (MRMC), the Armed Forces Health Surveillance Center (AFHSC), and USU. The Director regularly interfaces with SC members through monthly meetings via teleconference, as well as three in-person meetings each year. The SC provides important feedback and consultation on the scientific and administrative direction of the program.

The Director executes the IDCRP through his deputy, scientific directors, and support personnel, including operations/finance, data management,

and regulatory leads. The major day-to-day protocol activities and patient contacts are conducted by IDCRP team members at numerous Medical Treatment Facilities (MTF) around the world. Active duty service chiefs at the MTFs serve in critical roles as both a “chain of command” at a distance as well as Principal Investigators on research studies. In addition, regulatory oversight is conducted internally as well as in partnership with the NIAID Regulatory Compliance and Human Subject’s Protection Branch (RCHSPB). Moreover, to conduct its mission, the IDCRP partners with numerous different types of organizations, shown in the figure below.

The IDCRP as a Bridge Builder





Clinical Research Sites



Walter Reed National Military Medical Center (WRNMMC) at Bethesda

WRNMMC is a key clinical site for the IDCRP. Captain Timothy Burgess transitioned in September 2012 from his role as Deputy Program Director of the IDCRP to become the Chief of the Infectious Disease Service at WRNMMC.

IDCRP's Research Principal Investigators at WRNMMC are Drs. Anuradha Ganesan and Amy Weintrob. Both Drs. Ganesan and Weintrob have been with the IDCRP for over seven years, and are actively involved in protocols spanning the Program research focus areas. Dr. Ganesan has an interest in translational research, which includes the study of novel therapeutics designed to modulate the chronic immune activation observed in HIV-infected persons and the

use of molecular-based diagnostic methods to identify infectious diseases. In the past year Dr. Ganesan has received a DMRDP grant to study the role of molecular diagnostics in the diagnosis of invasive fungal infections. Dr. Weintrob's interests include the effects of genetic polymorphisms on HIV disease progression and response to antiretroviral therapy as well as studying infection and colonization with multidrug resistant bacteria in healthcare settings. In addition to her role as a PI at WRNMMC, Dr. Weintrob also serves as the Deputy Director of the Trauma Infectious Disease Outcomes Study (TIDOS) project.

The WRNMMC staff is comprised of a very diverse group of talent, skills and education, ranging from research assistants, administrative support, Clinical Research Coordinators (CRCs) to RN CRCs. There is a total of 19 IDCRP staff at WRNMMC.





Naval Medical Center Portsmouth

Naval Medical Center Portsmouth (NMCP), in Virginia is the oldest continuously running hospital in the Navy medical system. The site has been actively participating and enrolling in IDCRP protocols since 1998. For over six years (2007-12), the Infectious Disease Service has been led by CAPT Jason Maguire. CAPT Maguire also serves as the U.S. Navy Specialty Leader for Infectious Diseases and the Navy representative on the IDCRP Steering committee. He also serves as a reviewer for the IDCRP Scientific Review Board and, in line with his long-standing research interests in tropical disease, he serves as the Principal Investigator of IDCRP-037 Deployment and Travel Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies Among Department of Defense Beneficiaries (TravMil).

Rounding out the IDCRP leadership at NMCP are Research Physician, Dr. Tahaniyat Lalani and Site Manager, Rezalina Tant. Dr. Lalani joined the IDCRP in 2008 after completing her residency and fellowship at Duke University Medical Center in Durham, NC. Dr. Lalani is part of the clinical staff at NMCP and serves as an Associate

Investigator on IDCRP-037 (TravMil). Dr. Lalani's research interests include travel related infectious diseases, bacteremia and endocarditis.

Since 2007 the IDCRP research staff has been managed by Rezalina Tant, who brings with her 12 years of clinical research experience. Her team is comprised of CRCs, a Laboratory Research Assistant and Administrative Support. Within this group there is a wealth of experience and skill that fosters the research mission.

In the past year, NMCP implemented and completed enrollment for Shipboard MRSA, exceeded enrollment goals for the HIV Natural History Study, and remains one of the top enrolling sites in the ARIC Natural History Study. NMCP has also played a key role in implementing electronic data capture for IDCRP studies including IDCRP-057: Prevalence and Clinical Characteristics of Infection Caused by the Newly Emerging Pathogen, *Rickettsia parkeri*, RV-168 and ARIC.

The site welcomes CDR Karl Kronmann who took over as Head of the Division of Infectious Diseases in July 2012 after serving as the Officer-in-Charge at NAMRU-3 in Ghana for three years. His research interests include vector-borne febrile infections and influenza. He currently serves as the Site Principal Investigator for ARIC.





San Antonio Military Health System

The San Antonio Military Health System (SAMHS) Infectious Disease Service is led by LTC (P) Clinton Murray, who, along with the IDCRP staff and active duty researchers support the Program's activities in San Antonio. Charlotte Rhodes serves as the Clinical Site Manager, and manages a team of 20 staff. As one of the largest sites in the network the San Antonio team is very productive. This year, the IDCRP specimen repository, formerly located at Wilford Hall Ambulatory Surgical Center, was relocated to the San Antonio Military Medical Center (SAMMC). This transition was a part of the five year Base Realignment and Closure (BRAC) plan and positions this valuable program asset for ongoing use into the future.

The site has supported the HIV Natural History study for the past 20 years and continues to serve as one of the two major US sites enrolling and following patients in the Trauma Infectious Disease Outcomes Study (TIDOS). This work has generated several laboratory studies that the site is supporting in collaboration with the San Antonio Military

Medical Center's Department of Clinical Investigation laboratory. This work is supported by the IDCRP's molecular biologist, Katrin Mende, PhD and her team. The proximity of the SAMMC with the Institute for Surgical Research provides a key link for the collaboration on the TIDOS protocol.

SAMMC is also collaborating with the IDCRP team at Naval Medical Center San Diego to execute the Self-Administered Nasal Influenza Feasibility (SNIF) study, which was implemented in July 2012. This research, funded by the Military Vaccine Agency (MILVAX), represents a new partnership with one of the DoD's funding agencies with a more operational focus. The study team hopes to enroll 1100 participants with the primary focus in active duty military members. In addition to this new influenza vaccine work, the site continues to support the Natural History Study of the Acute Respiratory Infection Consortium (ARIC) at various locations on Fort Sam Houston.



Madigan Army Medical Center

The Madigan Army Medical Center (MAMC), in Fort Lewis, Washington joined the IDCRP network in 2010 in the wake of the H1N1 influenza pandemic. The IDCRP presence at the site was launched with the opening of the IDCRP-045 Natural History Study of the Acute Respiratory Infection Consortium (ARIC). Since then, MAMC has continued to support the respiratory disease portfolio by opening IDCRP-045-01 FlupRO, IDCRP-058 Retrospective H1N1 Case Review, and IDCRP-062 H1N1 Plasma Treatment. Site Investigator, Dr. Mary Fairchok, supports the Program's activities at MAMC along with the site's Clinical Research Nurse, Cindy Baker, and the Clinical Research Coordinator, Debra Angell. Dr. Fairchok has been at MAMC since 1994, as an active duty Army physician until her retirement in 2007. She joined the IDCRP in 2010. She is board certified in General Pediatrics and in Pediatric Infectious Disease and her research interests include respiratory viruses, immunizations and staphylococcal disease.



Tripler Army Medical Center

Tripler Army Medical Center (TAMC), in Honolulu, Hawaii has been involved in the HIV Natural History Study since the late 1990's. The IDCRP currently has one Clinical Research Coordinator, Mr. Torri Fuller, on-site recruiting, enrolling and following up with participants in the infectious disease clinic at TAMC. Because of its location "at the tip of the spear" in the Pacific region, the TAMC site holds significant potential for conducting other types of research, such as respiratory disease, travel-related illness and sexually transmitted infections.



Naval Medical Center San Diego

The Naval Medical Center San Diego (NMCS) is a major military medical treatment facility that is also a teaching hospital and research center. NMCS remains a productive site leading several multi-center IDCRP protocols and continues to support other ongoing research.

CDR Ryan Maves heads the Infectious Disease service where the IDCRP is housed. The IDCRP research group is supported by active duty ID physicians serving as research investigators.

CAPT Mary Bavaro is the Site PI for four prospective studies including the HIV Natural History study, START study, Plasma Treatment study for influenza as well as the newly opened SNIF study. In addition to her time as an IDCRP research investigator, CAPT Bavaro also serves as the NMCS Fellowship Program Director.

As the Principal Investigator, CDR John Arnold leads the Acute Respiratory Infection Consortium (ARIC) multi-site study for the IDCRP at NMCS. He is also an active and core member of the IDCRP ARIC Technical Advisory Group (TAG).

LCDR Mark Johnson is head of the Travel Clinic located within the Infectious Disease clinic and serves as the Site PI for the TravMil study. He is also the Assistant Fellowship Program Director.

There are a total of 10 IDCRP staff members working in collaboration with the active duty investigators at NMCS. Alona Diem is the Clinical Site Manager and is responsible for the day-to-day research operations in the clinic. The research team consists of a skilled and dedicated group of Clinical Research Coordinators, a Regulatory Affairs Coordinator as well as a Clinical Research Student.





Martin Army Community Hospital

Martin Army Community Hospital at Fort Benning, Georgia is our newest clinical research site. Maj Brian Lanier, a family practice physician, is the active duty point of contact. There are currently four staff on-site: Natasha Law, Tameka Smith, Arile Hadley and Oswald McCrory. Fort Benning has served as the location for a large scale clinical trial assessing hygiene-based prevention measures for skin and soft tissue infections in military trainees. With the assistance of the Defense Medical Research and Development Program and USU, research activities there will be expanding to include epidemiology and immunology of skin and soft tissue infections, as well as treatment effectiveness studies.



Landstuhl Regional Medical Center

Landstuhl Regional Medical Center (LRMC), in historic Landstuhl, Germany has served as the initial entry point and key linchpin for the Trauma Infectious Disease Outcome Study (TIDOS). Trauma patients who are medically evacuated from Afghanistan (Operation Enduring Freedom) receive care at LRMC prior to evacuation to the United States. IDCRP personnel on-site include research coordinators and microbiology technicians who begin tracking patient specimens and medical procedures as well as routinely interacting with active duty and other healthcare personnel involved in the care of patients with combat-related traumatic injuries.

Research Focus Areas

The IDCRP scientific program has seven major areas of emphasis, called Focus Areas. These are executed under the leadership of two scientific directors and their deputies. The relative size of these Program Areas varies, based on historical evolution of the program as well as specific military research imperatives and funding opportunities. The IDCRP strives to ensure the best science is being conducted that fills knowledge gaps that are relevant to the DoD population and their unique infection risks. More details on the current activities of these Program Areas, in addition to some key accomplishments from this past year, are noted in the following pages.

New protocol concepts continue to be vetted through the General Infectious Diseases or HIV/ STI Working Groups, whereas ideas for individual analyses within a protocol are vetted amongst study-specific team members.

- Trauma/Combat Related Infections
- Acute Respiratory Infections
- Operational Deployment/Travel Associated Infections
- Biodefense/Emerging Infectious Diseases
- Skin and Soft Tissue Infections
- Human Immunodeficiency Virus (HIV)
- Sexually Transmitted Infections



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Trauma/Combat Related Infections

Military personnel who have suffered combat-related traumatic injuries are at increased risk for infectious complications. Many of these infections are caused by multi-drug resistant organisms (MDRO) for which evidence-based recommendations for treatment and prevention are lacking. Moreover, as observed in ongoing military operations in Afghanistan (Operation Enduring Freedom), the nature and severity of some combat-related traumatic injuries (e.g., dismounted complex blast injuries due to improvised explosive devices) have been associated with an increase in severe wound infections caused by invasive molds, often necessitating aggressive chemotherapy and surgical procedures for cure. Descriptions of the epidemiology, risk factors and clinical characteristics of combat trauma-related infections are a major research focus area for the program, as they provide a knowledge base for clinical practice guidelines and future treatment and prevention trials. Ultimately, the results of these studies will broaden our understanding and improve the

clinical management and prevention of infection among personnel injured in the course of military conflict.

Now entering its fourth year of recruitment and enrollment, the “Departments of Defense and Veterans Affairs Multi-center Cohort Study evaluating Infection-Associated Clinical Outcomes in Hospitalized Medical Evacuees following Traumatic Injury (IDCRP# 024)” is the foundation of this focus area. This multi-site, observational longitudinal cohort study, known as TIDOS (Trauma Infectious Disease Outcomes Study), is the first prospective evaluation of infectious disease complications, risk factors, and long-term outcomes among military personnel who have suffered combat-related traumatic injury. Funded by the US Navy Bureau of Medicine and Surgery (BUMED) Wounded Ill and Injured Program and the NIAID, TIDOS represents a major collaborative effort between several MTFs [Landstuhl Regional Medical Center(LRMC), Walter Reed National

Military Medical Center (WRNMMC), and San Antonio Military Medical Center (SAMMC), DoD research commands, US Army Institute for Surgical Research (USAISR), Walter Reed Army Institute of Research (WRAIR), the St. Louis Veterans Administration Medical Center (St. Louis VAMC), and the Uniformed Services University.

Since the inception of the study, the TIDOS investigative team has contributed to the development of an Infectious Disease supplemental module in the USAISR's Joint Theater Trauma Registry (JTTR). The module has become a critical tool in the evaluation of combat trauma-related health event/outcome analysis secondary to infection complications, while also addressing performance improvement aims of the Joint Theater Trauma System. Through collaboration with the St. Louis Veteran's Administration Medical Center (VAMC), the study is also poised to capture the occurrence of long-term infectious complications among combat-injured personnel who seek care in the VA medical system. In addition to the clinical research objectives of the study, the establishment and utilization of a microbial specimen repository has allowed the growth and expansion of laboratory-based

investigations. A number of laboratory protocols are planned or currently ongoing, including studies on the epidemiology of antibiotic resistance, characterization of microbial virulence factors, and the evaluation of molecular diagnostic methods for invasive fungal infections.

The hallmark of TIDOS, and its major strength, is the ongoing collaboration among multiple institutions and study investigators from various disciplines, including infectious disease, trauma surgery, orthopedics, pathology, clinical microbiology and infection control. The breadth of knowledge of the investigative team has been critical in providing relevant subject matter expertise, as well as direction for future areas of investigation. Through this multi-disciplinary effort, data from the TIDOS will yield new insights and strengthen the current foundation of knowledge, from the molecular aspects of microbial pathogenesis to establishing clinical practice guidance for infection treatment and prevention. The fulfillment of these study objectives will have the ultimate benefit of improving the care of military personnel who have sustained combat-related traumatic injuries.

Highlights:

- Since study initiation in June 2009, approximately 1200 individuals have been enrolled in the TIDOS cohort
- A case-series investigation of invasive fungal wound infections (IFI) was completed and published in *Clinical Infectious Diseases*. The information from this investigation has been widely disseminated within the DoD medical community, and has contributed to the development of clinical practice guidance for IFI among wounded military personnel
- A multi-site, retrospective case-control study (IDCRP#044) was launched to assess risk factors associated with osteomyelitis, a major acute and long-term infectious complication of orthopedic injury



Beginning in 2009, physicians at Landstuhl Regional Medical Center (LRMC), National Naval Medical Center (NNMC), Walter Reed Army Medical Center (WRAMC), and Brooke Army Medical Center (BAMC) noted an increase in invasive fungal wound infections (IFI) among patients who had suffered combat-related traumatic injuries in Operation Enduring Freedom. Investigators on the IDCRP's Trauma Infectious Disease Outcome Study (TIDOS) conducted a case-series investigation in conjunction with orthopedic, trauma, and infectious disease services, identifying 36 cases of IFI in an 18-month period. The majority of the patients were injured by improvised explosive devices while on foot patrol in southern Afghanistan, and suffered lower extremity amputations requiring massive blood transfusion. Detailed characterization of these patients' findings and assessment of surgical and medical management was provided in a DoD Technical Report briefed to command leadership at facilities receiving these patients as well as senior military medical leadership. The study findings are described in Warkentien et al. "Invasive Mold Infection Following Combat-Related Injuries", published in *Clinical Infectious Diseases*. Ongoing research is focused on risk factor determination, methods to improve timely and accurate diagnosis, institution of preventive and early therapy to decrease morbidity, and refinement of evidence-based clinical practice guidance for IFI.





U.S. Navy Photo-MCS 2nd Class Pedro Rodrigues

Acute Respiratory Infections

Influenza and other agents of acute respiratory infection (ARI) possess tremendous epidemic potential and can cause substantial morbidity.

Treatment and prevention of ARI is of particular concern to the military; outbreaks of ARI pose major threats to the health and operational readiness of military forces in both deployed as well as recruit settings. Accordingly, rates of immunization of military personnel for influenza and adenovirus, historically the leading causes of ARI morbidity in military populations, remain consistently high. Yet, as recent years have shown, the effectiveness of immunization can be thwarted by the emergence of novel strains, underscoring the ongoing need to identify the major causes of ARI and to provide clinical and laboratory characterization of the illnesses they cause.

A global network of laboratory-based active surveillance for ARI has served as the foundation of ARI research activities in the DoD. These surveillance systems played a lead role in the identification of the pandemic 2009 influenza A (H1N1) virus, and are essential for the ongoing detection of ARI pathogens and description of disease trends. However, a number of critical knowledge gaps remained, particularly in the epidemiology and clinical characteristics of ARI among military populations. The Acute Respiratory Infection Consortium (ARIC), a multi-site, multi-disciplinary clinical research network for the study of ARI, was developed for this purpose. Now entering its fourth year of operation, the ARIC is comprised of five military treatment facilities and several DoD research laboratories, and is currently addressing multiple research objectives relating to the etiology, epidemiology, and immunology of ARI

among military personnel and their beneficiaries.

The clinical knowledge and expertise of the ARIC investigative team has facilitated the consortium's participation in clinical randomized controlled trials. The ARIC is currently participating in a NIAID-sponsored, multi-center protocol investigating the efficacy of hyperimmune plasma (IDCRP #062) for the treatment of severe influenza infection. In addition, through a grant provided by the US Military Vaccine Agency (MILVAX), the ARIC investigative team will be evaluating the effectiveness of self-administered influenza vaccine in a military setting (FluMist; IDCPR #070). Using immunogenicity endpoints, the trial will ultimately address whether self-administration of intranasal flu vaccine can achieve equivalent levels of protective immunity when compared to vaccine administered by a healthcare worker. The findings of this study will be invaluable in assessing whether this prevention strategy can be applied in the field, particularly among large numbers of deployed military personnel.

Highlights:

- After three seasons, 1100 adults and children have enrolled in the ARIC Natural History Study, and laboratory-based investigations of etiology and immunology are ongoing
- Recruitment and enrollment is ongoing in a multi-center clinical randomized controlled trial of hyperimmune plasma for the treatment of severe influenza infection
- An open-label, prospective clinical trial was initiated in August 2012 to evaluate the effectiveness of self-administered influenza vaccine
- Recruitment is ongoing to develop a symptom scale for severity of influenza infection



Vaccination is critical for the prevention of influenza, a major cause of acute respiratory infection (ARI) worldwide. Annual seasonal influenza vaccination is required of all military personnel, and is administered by qualified health care workers. In a military setting, particularly in times of rapid deployment, the self-administration of influenza vaccine with minimal health care worker supervision could ensure that personnel are immunized, while lessening the resource requirement for medical personnel. The same strategy of mass vaccination could be utilized among responders to epidemics/pandemics of influenza. To assess the feasibility of self-administered influenza vaccination, the IDCPR is conducting a Phase IV, open-label prospective trial at San Antonio Military Medical Center (SAMMC) and the Naval Medical Center San Diego (NMCSD) to compare the effectiveness of self-administered versus health care worker administered live attenuated influenza vaccine (FluMist®). Approximately 1100 subjects will be enrolled in this study, which will utilize safety and immunogenicity as the clinical endpoints for evaluation. The findings of this study are likely to impact the design and implementation of influenza prevention strategies in the DoD.



Operational Deployment/Travel-Associated Infections

The deployment of military personnel to international settings poses considerable health risks, particularly when these individuals enter environments endemic for certain infectious diseases. Deployment/travel-associated infectious disease threats include extremely common ailments such as infectious diarrhea and acute respiratory infection, as well as less common but potentially fatal vector-borne illnesses associated with fever, such as malaria, dengue or rickettsial disease. The primary objective of this research focus area is to identify the leading infectious disease threats that affect military operations, particularly during or following deployment. Through this research, an evidence base or prevention and/or therapeutic strategies can be established and effective DoD policy developed.

The “Deployment and Travel Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies among Department of Defense Beneficiaries (TravMil)” (IDCRP# 037) is currently active in three sites: the Naval Medical Center Portsmouth (NMCP; Portsmouth, Virginia), the Naval Medical Center San Diego (NMCSD; San Diego, California) the Walter Reed National

Military Medical Center (WRNMMC; Bethesda, Maryland). The establishment of a DoD Travel Medicine Research Consortium for the long-term study of travel- and deployment-related infectious disease threats provides a platform onto which new prevention and treatment strategies can be evaluated. In addition to the study of the epidemiology of these infections, the TravMil protocol also aims to evaluate current and new risk reduction and self-treatment strategies with regard to compliance, efficacy, cost-effectiveness, and side effect profile.

A key component of TravMil is an evaluation of the utility of molecular diagnostics of self-collected stool, blood, and oropharyngeal samples to determine the etiology of travel/deployment illness. If deemed effective and feasible, this diagnostic strategy may eventually be made available to forward deployed troops without access to advanced laboratories. Ultimately, information gained from this study will be used to improve the quality of care given in DoD travel medicine clinics, to eliminate ineffective interventions, and to provide region-specific infectious disease threat assessment for the DoD.

Acute infectious diarrhea is a well-recognized threat to deployed military personnel leading to significant short-term morbidity, potential for post-infectious sequelae, high levels of health care service utilization, loss of man-hours, and adverse impact on operational readiness of the deployed

force. In September 2012, IDCRP investigators initiated a randomized, double-blind, controlled trial (IDCRP# 065) to evaluate the efficacy of single-dose regimens with the most commonly used antibiotics adjuvanted with loperamide in the setting of watery traveler's diarrhea as well as azithromycin with and without loperamide in the setting of dysentery and febrile diarrhea. This multi-site collaboration is comprised of investigators from the Naval Medical Research Center (NMRC), Naval Medical Research Unit-3 (Cairo, Egypt), US Medical Research Unit-Kenya (Nairobi, Kenya), Department of Military Medicine, Royal Centre for Defense Medicine, Birmingham, UK, Naval Medical Center Portsmouth, Landstuhl Regional Medical Center, and the Uniformed Services University. The study will be conducted at three international sites: Camp Lemonnier, U.S. Naval Expeditionary Base, Djibouti; British Army Training Unit, Kenya (Nanyuki, Kenya); and UK Role 3 Joint Force Hospital, Camp Bastion (Afghanistan). Findings from this study will be critical in the development of clinical guidelines for the diagnosis and management of travelers' diarrhea among deployed military personnel.

Highlights

- TravMil recruitment and enrollment ongoing at three clinical sites, with >1000 individuals enrolled to date
- Enrollment begins in a randomized controlled trial for the treatment of traveler's diarrhea among US and UK troops stationed in Djibouti, Kenya and Afghanistan



In November, investigators on the IDCRP's Travel Medicine (TravMil) protocol hosted a symposium at the 2012 Annual Meeting of the American Society for Tropical Medicine and Hygiene in Atlanta, Georgia. Highlighting the primary objectives of the study, the symposium provided the following:

- 1) Overview of study methodology and participant demographics, destinations, travel risk levels and disease incidence, as well as the utility of serological diagnosis in ill returning travelers;
- 2) Review of utilization, compliance, reported side effects, and therapeutic effectiveness of self-treatment for traveler's diarrhea;
- 3) Review of destination-specific antimalarial prophylaxis prescription patterns and adherence rates stratified by medication prescribed and duration of travel;
- 4) Overview of the development of a multiplex PCR assay to detect common diarrheal pathogens including *Salmonella*, *Shigella*, *Campylobacter*, Enterotoxigenic *E. coli*, Enteraggregative *E. coli*, Enterohemorrhagic *E. coli*, *Giardia*, *Cyclospora*, *Cryptosporidium* and Norovirus.

Findings from this study will be instrumental in the development of clinical practice guidance in DoD travel medicine clinics, and in providing region-specific information on infectious disease threats to military personnel in deployed settings.

Biodefense/Emerging Infectious Diseases

Research on potential agents of bioterrorism is a critical component of the IDCRP mission. Agents of viral hemorrhagic fever, including Ebola and Marburg viruses, fall under this classification and have been the central targets of vaccine development. Ebola and Marburg infections are diseases of military importance, not only as potential bioterrorism agents, but also as threats to military personnel deployed to endemic settings. At present, there are no effective treatments and no licensed vaccines for Ebola or Marburg. Through a collaboration between the NIAID Vaccine Research Center (VRC) and military investigators, the safety and immunogenicity of an Ebola DNA and a Marburg DNA Vaccine was assessed at a Walter Reed Army

Institute of Research (WRAIR) collaborative field site at Makerere University in Kampala, Uganda (IDCRP# 022). The IDCRP has also conducted a laboratory-based, serologic study of military smallpox vaccinees (IDCRP# 026), assessing factors of host immunity that may attenuate the immune response to vaccination.

Other efforts in this research focus area include the study of emerging infectious diseases. The Tidewater region of Southeastern Virginia is home to the Gulf Coast tick, a known vector for *Rickettsia parkeri*. Rickettsial infections are a cause of acute febrile illness and are endemic in regions where tick populations (the vector for the pathogen) are prevalent. The Naval Medical Center Portsmouth (NMCP) is located in this region, and is the lead site for this current study, which aims to assess the prevalence and clinical characteristics of *Rickettsia parkeri* infection among adults and



children presenting to the hospital with acute febrile illness (IDCRP# 057). Investigations in this focus area also include a laboratory-based study of leptospirosis, a zoonotic bacterial infection common in many tropical climates (IDCRP# 065). Military personnel deployed to such settings are at increased risk for environmental exposure to and infection by *Leptospira*, and substantial morbidity and mortality can result.

Highlights

- Laboratory-based immunologic testing ongoing in a DNA vaccine trial for Ebola and Marburg viruses
- Recruitment and enrollment ongoing in a study of the prevalence and clinical characteristics of *Rickettsia parkeri* infection among adults and children with acute febrile illness

As a naturally occurring infection, smallpox was the target of a successful global eradication campaign in the 1950s and vaccination of civilian populations ceased. However, because of ongoing concerns of bioterrorism, the US military continues to operate a smallpox vaccination program for operational forces and health care workers. In the last decade, over one million individuals have received the vaccine, which is made from a smallpox-related virus called Vaccinia. In addition to conferring protection against smallpox, the Vaccinia virus has shown early promise as a vaccine-delivery system, inducing immunity to pathogens such as HIV. Because of its potential use in HIV candidate vaccines, investigators at the IDCRP and the Military HIV Research Program (MHRP), with support from the US Military Vaccine Agency (MILVAX), evaluated the impact of pre-existing immunity to Vaccinia in a cell-based infection model. Using longitudinal sera from military personnel who had been vaccinated, the investigators found that serum antibody responses to smallpox vaccination did not persist over extended periods of time (e.g. 5 years post-vaccination), suggesting that prior vaccination for smallpox might not interfere with the effectiveness of novel vaccines using Vaccinia virus as a vector.

Skin and Soft Tissue Infections

Skin and soft tissue infections (SSTI) frequently occur among military personnel, particularly in recruit training environments. Methicillin-resistant *Staphylococcus aureus* (MRSA), once confined to health care facilities but now a major cause of community-acquired SSTI, is of particular concern. Because outbreaks of MRSA can disrupt training cycles and interfere with military operations, the development and evaluation of MRSA prevention strategies remains a major priority for the military medical community. For the IDCRP, investigations to date have ranged from field testing of personal hygiene-based interventions to an evaluation of a *Staphylococcus aureus* vaccine candidate in a Phase I randomized controlled trial.

Studies of the epidemiology, prevention and control of SSTI, and of MRSA SSTI in particular, are an ongoing component of the IDCRP research portfolio. In spring 2012, IDCRP investigators completed a cluster-randomized trial (IDCRP# 055) for the prevention of MRSA SSTI among military trainees at Ft Benning, Georgia. In addition to the evaluation of the investigational product, a chlorhexidine-based body wash, the study also supported a number of secondary objectives, including the assessment of point-of-care rapid diagnostics, a study of the natural history and immune response to SSTI, and estimates of the cost-effectiveness of MRSA prevention strategies in the military health care system. Analyses of the primary and secondary endpoints are nearing completion. The results of these studies, conducted among a population of military recruits at increased risk for SSTI, are likely to influence the formulation of DoD policies regarding the prevention of MRSA SSTI in the military.

The current understanding of MRSA SSTI epidemiology and pathogenesis has been greatly aided by the utilization of molecular techniques, namely the characterization of pulsed-field type (PFT) among clinical isolates of MRSA. Differentiation of MRSA strains by PFT may yield important insights on the epidemiology of disease, particularly as it relates to colonization, transmission and risk for infections such as cellulitis and abscess. Analysis of MRSA PFT is underway among clinical isolates obtained in the recently completed trial at Fort Benning. Similar strategies are being employed for isolates obtained in a MRSA prevalence study in a shipboard setting (IDCRP #068).

Other laboratory-based investigations of MRSA epidemiology are planned. For example, as part of an observational study to investigate the clinical and molecular epidemiology of MRSA among recruits at Fort Benning (IDCRP #074), investigators will be examining the relative abundance and distribution of non-*Staphylococcus aureus* bacterial species among individuals with and without SSTI. Findings from these investigations may prove beneficial in elucidating the pathogenesis of SSTI and identifying factors that put individuals at risk.

Highlights

- Completion of a cluster-randomized trial (> 30,000 recruits) for the effectiveness of chlorhexidine-based body wash against MRSA SSTI among military recruits at Fort Benning, Georgia
- Initiation of an observational study to characterize the clinical and molecular epidemiology and to estimate the cost burden of MRSA SSTI among military recruits (IDCRP #074)
- Ongoing laboratory-based investigations to determine MRSA pulsed-field type (PFT), a marker of strain virulence, among clinical isolates and to describe factors of microbial ecology that may influence risk of disease



Photo: Major Kirk Waibel, MD

Skin and Soft Tissue Infections

Military recruits are known to be at high-risk for skin and soft tissue infections (SSTI), and an increasing frequency of cases are caused by community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). Knowing the etiology of SSTI is important for the selection of optimal treatment regimens. However, current diagnostic methods require culture of wound specimens which in some cases (e.g. non-purulent cellulitis) may be difficult to obtain. IDCRP investigators are currently conducting studies of SSTI etiology and immunology among military recruits at Fort Benning, Georgia. LTC Michael Ellis, principal investigator, was the recipient of the 2012 Uniformed Services University of the Health Sciences (USUHS) Program Grant, a 3-year, \$2.1M award that will support novel research efforts in this area. This project will utilize culture-independent techniques for the determination of SSTI etiology in the context of a cellulitis treatment trial. The treatment trial will directly support clinical practice guidance on the optimal antibiotic regimen for management of cellulitis, an extremely common infection among military personnel. In addition to the primary endpoints of the trial and evaluation of diagnostic methods, the study will also examine factors of host immunity to SSTI, as well as molecular characterization of clinical and colonizing *S. aureus* strains and the identification of *S. aureus* virulence factors.



Human Immunodeficiency Virus (HIV)

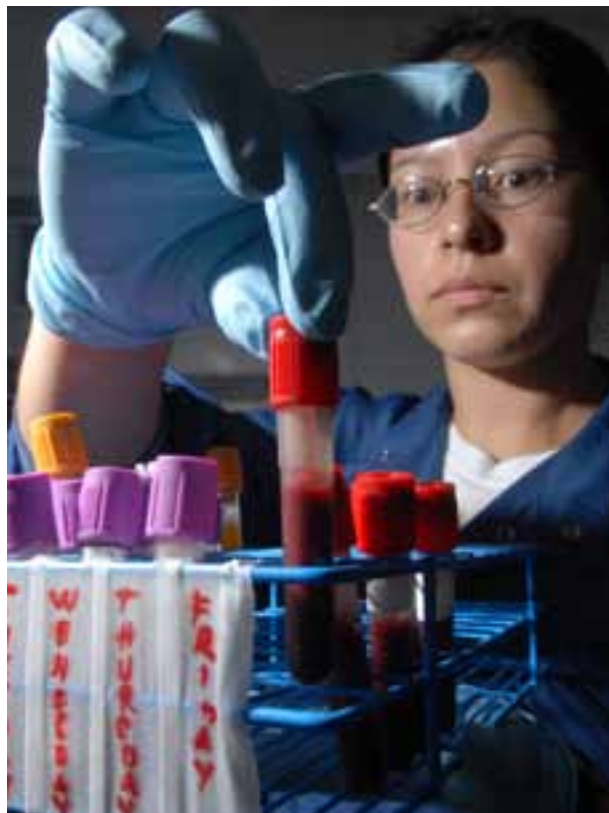
Human immunodeficiency virus (HIV, the virus that causes AIDS) infection among active duty soldiers, sailors, airmen, and marines occurs at a lower rate than in the civilian population; however it has important consequences for personal health and serious impact on readiness and military service. Those with HIV are not allowed to enlist into active duty service; however, since the beginning of the HIV epidemic, over 10,000 military members have been diagnosed with HIV while on active duty. Military policy limits these troops from being able to deploy to combat zones and from certain jobs, however most of these individuals may continue to serve as long they remain healthy (many have done so a decade or longer). In order to ensure continued fitness and care, HIV infected active duty members are required to undergo medical evaluation every six months at a military treatment facility. Leveraging these

visits, the U.S. Military HIV Natural History Study (NHS, see also box on page 30) has been enrolling subjects since 1985 to investigate HIV in the military setting, collecting data and specimens. Since 1996 when effective treatment of HIV with antiretroviral medications became possible, the course of the disease has been dramatically changed from being a death sentence for many (over 1700 active duty members have died of HIV, most before 1996) to a chronic disease. The NHS and IDCRP HIV research program have successfully adapted to this major shift, embracing a new focus on the health, longevity, and function of HIV infected active duty and other military beneficiaries while also reinvigorating the focus on prevention of new HIV infections. Neurocognitive disease in HIV infected active duty members continues to be an important IDCRP research area (see box on page 31) given the military policy focus on this complication.

HIV research is the longest standing component of the IDCRP portfolio and a vibrant and highly productive focus area. Building on a well-established body of descriptive research, the HIV program

has matured to successfully complete several prospective studies, to leverage unique resources to build collaborations with field-leading experts, and to continue to respond to advances, addressing prescient questions in HIV clinical science. In this past year we completed a large multi-site cohort study with a nested randomized trial as well as our first collaborative international HIV study, presented 19 abstracts at national/international meetings, had 16 manuscripts published/accepted, and importantly received an award of \$7.1M of additional funding for the next three years. Collaboration, both within and outside of the DoD, is a strength of the program, as evidenced by more than 30 investigators from 19 institutions, and new relationships continue to be developed. Strategic partnerships have been cultivated with the U.S. Military HIV Research Program (MHRP), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), and Veterans Aging Cohort Study (VACS).

The broad ranges of efforts from our four HIV research program areas are described and highlighted below with examples:



HIV Long Term Health

Understanding, predicting, and preventing negative consequences of HIV infection relevant to active duty service members and DoD beneficiaries.

Understanding the clinical consequences of HIV infection has been the focus of the HIV NHS since its inception and a key HIV research program area since formation of the IDCRP. Since the availability of effective HIV treatment, the clinical consequences of infection have shifted from being primarily AIDS (e.g. opportunistic infections, cancers, dementia) and death to what has been termed serious non-AIDS (SNA), although the former remain important because of their severity. SNA comprises a multitude of organ system complications thought to arise directly or indirectly as a consequence of HIV infection and its activation of the immune system. For example, cardiovascular disease (CVD) has become the leading cause of mortality among those in the developed world with HIV infection and while this mirrors the broader population, heart attacks (MI) occur more frequently and at a younger age than in those without HIV. While MI are still not common among HIV infected active duty, the foundation for later events appears to be laid during this period. Early identification of risk will allow preventive interventions and enhanced screening to avoid the potentially devastating outcomes of CVD among our beneficiaries.

As part of our effort to understand HIV outcomes, the IDCRP has partnered with Veterans Administration (VA) researchers to understand SNA as well as AIDS and death among those with HIV. Similar to the NHS, the Veterans Aging Cohort Study (VACS) studies veterans with HIV infection over time. Importantly, service members who are HIV infected while on active duty often enter the VA healthcare system after leaving active duty. Together with our VACS colleagues, we are capitalizing on the DoD and VA single payer healthcare systems with centralized databases to create a cohort of subjects with extensive follow-up. This resource will offer the chance to investigate long

term outcomes of early clinical decisions as well as the predictive value of various measures including biomarkers.

An exciting area of study, biomarkers have been identified in association with a number of HIV associated conditions as well as linked to outcomes including AIDS and death. Two of these markers, interleukin-6 (IL-6) and d-dimer, markers of inflammation and coagulation respectively, have been strongly associated with HIV outcomes including cardiovascular disease, AIDS, and death. Working with VACS experts from the Universities of Pittsburgh and Vermont, we have developed a new protocol leveraging unique DoD resources to investigate whether the elevation of these biomarkers returns to a pre-HIV level in HIV infected active duty members treated effectively with highly active antiretroviral therapy (HAART) and to understand how this is linked to outcomes including cardiovascular disease, AIDS, and death. At the same time, we are collaboratively investigating an index developed within the VACS to predict HIV outcomes and have validated this index in our population. Importantly, we also showed that some tuning

of the model is needed in this younger, healthier group, a population that was largely lacking from the original model development. These results were presented at an international workshop, an initial manuscript is near submission, and the next step in model recalibration is being planned.

Finally, in collaboration with the Atlanta VA, we are investigating the cost effectiveness of HIV care in the military and VA. Relevant to the current debate about the U.S. healthcare system and how best to provide care to all of our citizens, this study will evaluate important questions about the cost benefit of population HIV screening, early initiation of antiretroviral treatment, and the effects of IV drug use and homelessness. Comparison with civilian healthcare system data is planned and will allow inferences to be drawn about the cost benefits of centralized, single payer healthcare in the U.S. Initial findings from this work, presented at an international workshop and submitted for publication, demonstrate that HIV outcomes in response to HAART are very good in both settings, but somewhat better in the DoD. Much of this difference appears to be explained by population differences (the VA population is older, more ill, and has more homelessness and IV drug use) but even after accounting for these, differences remain and are being investigated further.



HIV HAART Outcomes

Understanding when and in whom to start HAART and how to maximize the long-term benefits of treatment while minimizing adverse effects.

While treatment of HIV infection with HAART is a central component of ensuring long term health, investigating optimal use of these agents, including outcomes and complications of prolonged therapy, necessitates separate attention and focus. One of the central questions of HIV clinical care at present is when to start HAART? Primarily guided by levels of key immune cells in the blood called CD4 or T-helper cells, clear evidence has shown that initiation of therapy before the development of AIDS or



a CD4 count below 200 cells/mm³ results in better outcomes. More recent studies have demonstrated that starting above 350 cells/mm³ is beneficial and this level has been accepted worldwide. In the past two years, a number of papers have been published including one from the IDCRP addressing whether starting HAART above 500 cells/mm³ is beneficial. Because there is controversy, a randomized trial is needed to definitively answer this question and a large multinational, multisite study is being conducted by INSIGHT. This study, called the Strategic Timing of AntiRetroviral Therapy (START) trial, has already enrolled the majority of the planned 4000 subjects. Four IDCRP sites (WRNMMC, SAMMC, NMCSO, NMCP) are enrolling subjects in this trial with funding support coming from INSIGHT. Additionally, several IDCRP investigators are active participants in the INSIGHT network; this has resulted in new collaborations as well as increased visibility of the IDCRP HIV research program in the academic community.

Investigations of HAART outcomes in the NHS have included clarification of the effect of race on outcomes. The literature is replete with reports that being a person of color is associated with a decreased response or poorer outcomes from treatment with HAART, but the authors acknowledge that unmeasured confounders such as education, income, and access to healthcare make definitive conclusions difficult. We have produced a series of manuscripts to investigate whether such clinical differences are evident in the military setting, where all have open and equal access to healthcare

and active duty have at least a high school education and a stable income. Our results show no evidence of differences in clinical outcome between blacks and whites starting HAART, although one study did find that it took longer for black subjects to fully suppress the HIV virus. This finding prompted a follow-on collaborative study with Vanderbilt University to investigate the contribution of HAART drug metabolism gene differences and we recently submitted a manuscript reporting that gene differences did not explain the race group difference. This leaves open the question of racial differences in either provision of or adherence to therapy. A recently submitted manuscript shows no difference between whites and blacks in the timing of HAART initiation according to guideline recommendations and racial associations with adherence are being actively studied in collaboration with investigators from Drexel University.

A number of additional investigations into HAART response are ongoing including studies of genetic and immunologic associations, effects of co-infections such as with hepatitis B, and pharmacologic interactions with other drugs. An IDCRP study published last year demonstrated that use of first generation antiepileptic drugs (AED) resulted in more frequent virologic failure among those on HAART. Important for many countries in the developing world, these data were immediately incorporated into the American Academy of Neurology and international guidelines. This year marked publication of the subsequent IDCRP study which demonstrated pharmacologic differences in



blood levels of the antiretrovirals resulting from first generation AED use, confirming the findings. At the same time another IDCRP investigation of the effects of co-infection with hepatitis B on HAART outcomes, in our open access healthcare setting with minimal IV drug use and racial diversity, has demonstrated that those with chronic hepatitis B have nearly double the chance of AIDS or death compared with those who do not. This clarifies the answer to this question in the literature and reinforces the need to aggressively prevent infection with hepatitis B using approved vaccines and for those who are co-infected, to encourage treatment according to guidelines.

HIV Novel Therapeutics

Improving outcomes of HIV-infected military members through the conduct of treatment trials with approved and novel agents and strategies.

Many studies have demonstrated the life saving benefits of HAART to treat infection with HIV. However a growing body of clinical experience and medical literature show that antiretroviral therapy

alone does not fully restore health at least in some individuals. In spite of viral suppression below the limit of detection, some patients continue to have levels of immune activation and inflammation above those who are uninfected. This is thought to directly contribute to fragility and premature aging, complications such as cardiovascular and kidney disease, and persistent susceptibility to some types of infection. Neurologic disease, no longer HIV associated dementia but rather subclinical cognitive and motor impairment, is also a concern of particular military importance given the need for high levels of performance from those in active duty roles. IDCRP novel HIV therapeutics research seeks to explore the use of new treatments and new uses for approved treatments in order to mitigate the ongoing damage caused by HIV as well as delaying the need for initiation of antiretrovirals, medications that carry their own toxicities and long term adverse effects.

The completion and publication last year of our pilot trial of atorvastatin, an approved cholesterol lowering drug with anti-inflammatory properties, added to the significant interest surrounding this class of medications as potential adjunctive therapy

for HIV infection. A larger multisite IDCRP trial is now being considered to investigate the use of this medication, in those starting or already taking HAART, to understand whether levels of immune activation and inflammation can be further reduced, immune restoration can be improved, and ultimately whether adverse clinical outcomes can be prevented.

Another collaborative pilot protocol currently in IRB review will investigate whether the use of rifaximin, an oral antibiotic that is not absorbed, can lower immune activation by decreasing the amount of bacteria in the gut. A series of studies from other institutions has demonstrated that immune cells in the gut are rapidly depleted during early HIV infection and there is evidence of increased movement of gut bacteria into the bloodstream associated with higher levels of inflammation. A causal link has been hypothesized and if correct, this translational study in collaboration with NIH and the University of Pittsburgh holds the possibility of building clinical evidence toward a new paradigm for treating HIV. There is significant enthusiasm about this approach and the NIH Clinical Center has provided a Bench to Bedside grant that will help fund this trial.

With a population of otherwise healthy, ethnically diverse HIV patients who are diagnosed and entered into care early after their infection, the IDCRP is ideally poised to continue to explore these avenues. We continue to seek additional opportunities and have had exploratory discussions with those working on therapeutic HIV vaccines, injections that would stimulate the patient's immune system to fight and control HIV. We are also working with others at USU, MHRP, the Center for HIV/AIDS Vaccine Immunology (CHAVI), Emory University, and the Harvard Broad Institute to study elite controllers and long term non-progressors, those individuals whose bodies naturally control the HIV virus or who do not show evidence of disease progression even after ten years of infection, to better understand the immune systems and genetics of these individuals in hopes of finding clues to inform HIV vaccine development and other therapeutic pathways.

HIV Prevention

Preventing new HIV infections among active duty members through understanding of acquisition and effective methods of prevention.

Preventing HIV infection is the most effective way to avoid its complications. Using the NHS to understand risk factors, the IDCRP has worked over the past several years to study the epidemiology of sexually transmitted infections among those with HIV. A series of investigations has delineated the high rates of infections with hepatitis B, syphilis, gonorrhea, chlamydia, and herpes in this population, all markers of ongoing sexual risk. Taken with the continued occurrence of 200-300 new HIV infections per year among active duty members, there remains a need for continued vigilance in prevention and investigations of new and novel ways to strengthen this effort. It is worth noting that military HIV acquisition rates are much lower than in the civilian population, suggesting that current prevention efforts are having a beneficial effect. In order to enhance the effectiveness of these efforts and further lower HIV acquisition rates, previous studies have shown that focally targeting prevention messages and interventions to those at highest risk of HIV infection is necessary. With the repeal of the "Don't Ask, Don't Tell" policy, there is now the opportunity to gather essential information about behavioral risk factors for HIV acquisition that will allow trials of targeted prevention. A new IDCRP study to accomplish this research is being designed and a follow-on protocol to investigate networks of HIV transmission is being planned. Data from these studies will facilitate the design and implementation of future IDCRP HIV and STI prevention trials. In parallel and in response to an inquiry from the Navy Marine Corps Public Health Center, we have planned an investigation of a proven effective intervention to prevent STI among those already infected with HIV called Partnerships for Health. This intervention has been vetted with Navy leadership, but data about how best to employ it in the military setting are needed. If successful, our hope is that results could inform a policy decision toward broad implementation and enhanced prevention.

U.S. Military HIV Natural History Study (NHS)

This protocol studies human immunodeficiency virus (HIV, the virus that causes AIDS) infection among active duty soldiers, sailors, airmen, and marines. HIV infected troops must have health and fitness evaluations at least every six months. The NHS was designed around this policy and since 1985 has enrolled over 5400 subjects, capturing their clinical and laboratory data as well as building a repository of specimens that has been recognized as “a national resource”. Many major advancements in HIV science relevant both to the military and civilian populations have been the result of this study including the first clinical staging system, understanding and characterization of clinical consequences of infection, as well as key host genetic factors related to infection and progression, evaluation of new and novel treatments, and many others. Over 300 peer reviewed publications in the medical literature have presented these cardinal findings.

Since effective treatment became available in 1996, the NHS has adapted its focus to preserving long term health and function of HIV infected troops by understanding, treating, and preventing the long term complications of the infection and its treatment. These complications are myriad, including premature aging, cardiovascular disease such as heart attacks, kidney and liver disease, cancers, bone loss, and neurologic disease, and the NHS is actively investigating all of these with the goal of being able to mitigate risk, both through effective treatment, but also by predicting

who is at risk and allowing prevention of adverse outcomes.

Prevention of HIV infection is the most effective means to avoid its complications and with 200-300 new active duty infections still occurring each year (a much lower rate than in the civilian population) and the repeal of the “Don’t Ask, Don’t Tell” policy, a new NHS sub study to investigate risk factors for HIV acquisition is being developed to better inform prevention programs. Finally, for those already HIV infected, a “functional cure” is being aggressively sought by the scientific



community. The NHS is contributing to this through the study of elite controllers and long term non-progressors, those whose immune systems are naturally able to control the HIV infection or who do not have complications even after ten years of infection, and by assessing clinical outcomes of potentially novel treatments. The IDCRP HIV Natural History Study continues to be a vibrant and productive investigation with relevance to our military and to other military and civilian populations around the world.



Prevalence and Predictors of HIV Associated Neurocognitive Disorders

Since the first identification of HIV infection among active duty troops and observation of the severe consequences of HIV associated encephalopathy and dementia (HAD), there has been concern voiced by military leadership about the function and readiness of HIV infected troops. This has resulted in a policy that allows continued service, but restricts such individuals from some roles such as piloting aircraft. Although HAD has become rare since the advent of HAART, cognitive and motor dysfunction can be detected in some HIV infected patients, even those on HAART. Data are needed to revisit this policy and until those data are available, duty restrictions remain in place.

Last year, the IDCRP completed its initial study of neurologic disease among those with HIV in the military and this year we have published the results in a series of three papers. The primary findings from the study demonstrated that even mild-moderate neurocognitive impairment was infrequent among military HIV patients, regardless of whether they were early or later in the course of the disease, and the rate of measurable impairment (assessed by approximately four hours of testing) did not differ compared to a military HIV negative control group. Importantly, 19%

of subjects did show some evidence of neurocognitive impairment and while this rate was not different from those without HIV, detection and diagnosis is essential to offer the best possibility of treatment. The ability to screen for these subtle conditions is currently impeded by the duration and intensity of testing required. Our second publication looked back at the components of the neurocognitive tests that were administered and demonstrated a moderate sensitivity and specificity, 73% and 83%, for detection of deficits with only an 11-minute testing battery and this was improved to 86% and 87% with an 18-minute battery. While these levels are not yet sufficient for widespread clinical use, this promising proof of concept study will be followed by a new IDCRP protocol investigating the use of biomarkers to aid diagnosis. Our third publication identified the importance of sleep as part of neuropsychiatric health. Surprisingly, 46% of subjects had insomnia and in many cases this was associated with depression. Nearly a quarter of those who had insomnia reported a decrease in activities of daily living. This study concluded that monitoring patients for depression and insomnia and addressing these may improve function. Further studies are being planned.



Sexually Transmitted Infections

Understanding the current STI threats to our active duty troops and how to effectively prevent, diagnose, and treat them.

Sexually transmitted infections remain a significant problem for our active duty forces and there has been a reemerging awareness among military leadership of the importance of the diseases caused by these infections including the need for current surveillance information, modern diagnostic capabilities, pathogen-focused treatment options, and optimized prevention including behavioral interventions and vaccines. The IDCPR has positioned this developing research program to address these needs and has begun active investigations with the goal of providing actionable data to inform military public health policy.

The foundation of clinical research is a detailed understanding of the epidemiology of disease.

To this end, we have forged a strong partnership with the Armed Forces Health Surveillance Center (AFHSC), joining the IDCPR research expertise, personnel, and clinical populations with the expert knowledge, skills, databases and other assets of the AFHSC Global Emerging Infections Surveillance & Response System (GEIS) network in support of the missions of both organizations. The first prospective STI study undertaken by the IDCPR and funded by AFHSC is a collaborative effort to characterize the prevalence and risk factors for antibiotic resistant gonorrhea among symptomatic military members.

Gonorrhea has long been a plague of militaries and the bacteria causing the disease have become increasingly resistant to antibiotics used to treat the infection. Now recognized as a worldwide

problem, some strains of the gonococcus (GC), as it has been called, have become resistant to the last reliable class of antibiotics, cephalosporins, used against it. A growing number of GC isolates have been reported to have resistance to all available antibiotics, posing a serious challenge to eradication and cure. Although surveillance data are developing in the United States and abroad to define the prevalence of this emerging threat, it is essential to understand this in our military population which is comprised of young individuals at high risk of infection who are routinely deployed and assigned to bases in the U.S. and around the world. This results in unique population mixing and the opportunity for increased acquisition and spread of pathogens such as GC.

Initially involving four geographically diverse bases (Ft. Bragg, NC; Ft. Carson, CO; Ft. Sam Houston, TX; and Ft. Lewis, WA), the IDCRP GC Resistance Study has been established in order to broadly sample high risk active duty members from STI clinics who have symptoms of infection and establish the prevalence of and risk factors for resistant GC. Already enrolling subjects at Ft. Bragg, the other sites have received IRB approval and are expected to open soon. Funding for additional sites at Naval Medical Center San Diego and Naval Medical Center Portsmouth has been requested from AFHSC for the coming year in order to evaluate the prevalence of this pathogen among Navy populations frequently deployed aboard ships. Data will be collected centrally at the IDCRP Data Coordination Center (DCC), routinely shared with AFHSC, and contrasted with results from similar AFHSC sponsored studies in Peru, Kenya, and Djibouti. Additional international sites are being pursued and it is planned that these data will be shared with the CDC Gonorrhea Isolate Surveillance Project (GISP).

An important component of the IDCRP GC Resistance study is the ability to culture and test the GC bacteria for antimicrobial susceptibility. While this capability was once a hallmark of military microbiology, new molecular tests to diagnose GC infection have supplanted culture, being simpler, less invasive, and less resource intensive.

As part of the IDCRP protocol, a new culture method is being assessed in hopes of simplifying isolation of the organism. At the same time a new susceptibility testing capability is being developed at USU with the goal of developing the military reference center for GC resistance evaluation. For at least the first year, training and GC characterization will be conducted by the University of Washington, a long standing gonorrhea reference center. In parallel, a companion AFHSC-sponsored investigation seeks to evaluate a new molecular test to identify GC resistance and if successful, this diagnostic tool could be implemented as part of the IDCRP protocol.

The GC resistance study is also an important part of the growing IDCRP STI research effort which has established clinical investigation among a high risk, HIV negative population as well as building relationships with care providers, leadership, and investigators in these clinics. Providing rich input to inform the development of new studies, such resources also markedly facilitate further planned investigations of other STI, novel diagnostics, treatments, and prevention interventions. We value the collaboration with our clinical partners and look forward to future work together.



Scientific Support

Every successful research endeavor, especially one that is multi-center such as the IDCRP, relies on strong logistics. In tandem with the science, the program has a number of different critical support teams to ensure success. These encompass operations, human resources, finance, as well as regulatory affairs and data management. In addition to some of these functions being provided by the Henry M. Jackson Foundation headquarters, the IDCRP has utilized a blended model wherein many of these functions are embedded directly within the IDCRP. These critical support functions are often behind the scenes, but they provide the foundation to allow the research teams to focus on science. In addition, the IDCRP has found it beneficial to have some of the support at the PCC and some “forward-positioned” at the research sites.

Data Processing

The Data Coordination Center (DCC) is the home of the IDCRP’s SAS and Oracle programmers, data system designers, data managers, data entry staff, and IT special projects manager. This group provides expertise to principal investigators for the conceptualization, design, collection, management, analysis, and publication of research study data. The DCC achieved many significant milestones this year, indicative of its growth and its critical role for ensuring IDCRP’s development as a premier clinical research organization.

The DCC sustained its efforts to become self-sufficient as the data services branch of the IDCRP. The DCC’s primary physical location was changed from its colocation with the Walter Reed Army Institute of Research’s Military HIV Research Program Data Coordinating and Analysis Center (MHRP DCAC) to the new IDCRP headquarters in Rockville. Further, the DCC’s sharing of MHRP’s computer systems have been reduced throughout the year, with the last from MHRP’s data management system to our own accomplished in September. The DCC currently shares one remaining system with the MHRP; this system is expected to be retired in FY2013. In addition, the IDCRP’s maturing biostatistics staff, who are responsible for performing data analysis and participating in the creation of manuscripts and abstracts, allow completion of all statistical work in-house. As a result, all statistical work has now transitioned from



Edward Parmelee, MS
Chief, Data Coordination Center

the University of Minnesota’s Data Analysis Center. At present, DCC personnel work at two locations: the IDCRP’s headquarters in Rockville and the San Antonio Military Medical Center (SAMMC).

The DCC continues to increase its utilization of Electronic Data Capture (EDC) as the standard methodology for clinical data acquisition and management; our primary application for this is ClinPlus. However, the team is also exploring new technologies, which will allow us to collect and manage data where it was not practical to do so previously. In September, one of the IDCRP’s studies implemented utilization of tablet



computers. These tablets are used at forward military sites, where use of traditional paper-based CRFs or desktop computers would be difficult or prohibited. Since the tablets are able to connect to the internet, study personnel now will have access real-time data.

Significant personnel transitions within the team include Kim Blankenship, who was promoted to Data Management Team Lead, and Chris Olsen, who was promoted to Oracle Programming Team Lead. The DCC roster also expanded with new hires of SAS programmers and an Oracle programmer to keep up with the burgeoning workload. In addition, the biostatistics group hosted several interns over the summer, some of whom have transitioned to full-time employment at IDCRP.

Mr. Edward Parmelee joined the IDCRP in July to lead the DCC. Ed has many years of experience in clinical research data management as well as a Master's degree in Epidemiology. Therefore, his broad experience and education will enhance and facilitate the DCC team's increasing capabilities and efficiency of operations.

Plans for the new fiscal year include: institution of InetSoft as the primary reporting tool for data management metrics and study status; exploration, adoption and implementation of a secure, web-based subject registry system; approval for and utilization of a Personal Identification Information (PII) and Protected Health Information (PHI) server within the .MIL environment at SAMMC; and, preparation for the DCC to successfully manage the data requirements of FDA-regulated studies.

The IDCRP underwent restructuring this year. As part of this, in June the biostatistics personnel were tied directly into the scientific working groups. The DCC continues to maintain a successful, collaborative relation with the biostatisticians. Also, in recognition of the organizational changes and to emphasize the team's increasing self-sufficiency away from MHRP, expertise, and greater emphasis on IDCRP data management services, the Data Coordination and Analysis Center (DCAC) was rebranded as the Data Coordination Center.





Regulatory Affairs

The IDCRC Regulatory Affairs team consists of staff at the network's Military Treatment Facilities and IDCRC Program Coordination Center (PCC). They perform essential duties throughout the IDCRC and are led by the Head of Regulatory Affairs. Staff assist in protocol development, conduct intensive review of IRB submissions to check for compliance with federal, local and IRB policies and procedures, consult with investigators during IRB review, coordinate with IRB staff to address any concerns, perform on-site quality assurance and auditing, track study milestones and maintain regulatory documents for the program.

The Head of Regulatory Affairs at the IDCRC PCC, often in collaboration with the NIAID Regulatory Compliance and Human Subject's Protection Branch (RCHSPB), conducts a thorough review of all IDCRC studies to ensure protocols are ready for ID IRB review. The rigorous review focuses on ensuring regulatory integrity, compliance with local, federal and USU regulations and procedures, and consistency within the protocol and informed consent documents. The aim of this

review is to provide the ID IRB with a high quality submission and reduce the post-review stipulations issued by the IRB. Provisions are made to review all research protocols and amendments, consent and HIPAA documents, recruitment material and case report forms for human subjects considerations.

Early in the protocol development stage, Regulatory Affairs staff and study monitors begin to refine the protocol and its associated documents in preparation for IRB review and study execution. RCHSPB serve as monitors of prospective, greater than minimal risk IDCRC protocols. The monitoring ensures the protection of human subjects, validates the integrity of data collection and capture, compliance with ICH/GCP and applicable regulatory bodies.

The USU ID IRB

The USU Infectious Disease Institutional Review Board (ID IRB) is a DoD Infectious Diseases community IRB centered at USU. The ID IRB was established via a Memorandum of Understanding (MOU) in January 2008. This MOU, signed by the Assistant Secretary of Defense (Health Affairs), the Surgeons General for each service, and the President of Uniformed Services University, created

a single review pathway for multicenter ID research, eliminating the need for multiple and repetitive scientific, ethical and second level reviews. Having this streamlined review process effectively made possible multicenter collaborative research without the delays of the past.

The ID IRB composition ensures local representation via the inclusion of members representing military treatment and research facilities participating in the IDCRP as well as additional members who provide representation and/or advocacy for particular subgroups. The ID IRB is headed by CAPT Trueman Sharp, Chairman of the Department of Military and Emergency Medicine at USU. CAPT Sharp chairs a diverse group of individuals from a variety of scientific and non-scientific backgrounds. ID IRB members are drawn from military medical centers from across the United States and the National Institutes of Health. Scientific board members hold expertise in fields that include Preventive Medicine, Pediatric and Adult Infectious Diseases and Immunology. The backgrounds of the non-scientist members range from enlisted service members to chaplains. The ID IRB is further supplemented by USU General Counsel and consultants who are authorities in clinical and research bioethics. With these resources and a unique military perspective behind them, the ID IRB fulfills its duty in safeguarding the rights and welfare of human subjects.

The military services' mandate for second level ethical review of human research is met by the Office of the Under Secretary of Defense for Personnel and Readiness USD(P&R)/ Triservice Headquarters Panel (HQ Panel). This HQ Panel provides administrative review of ID IRB determinations of FDA-regulated, greater than minimal risk and international research. Due to the collaboration of service representatives and USD(P&R), the HQ Panel eliminates the need for separate reviews by USD(P&R) and each participating service.

By consolidating the number of required reviews for multicenter research, the ID IRB has served



Maya Brown
Head of Regulatory Affairs

an integral role in the IDCRP's ability to ensure a coordinated research effort across the different services and DoD beneficiary population, as well as its evolution as new threats are identified. To further streamline its processes, USU employs an electronic protocol submission and review system (IRBNet) to automate much of the previously paper-centric IRB procedures. Since its creation, the ID IRB has reviewed over 60 domestic and international research protocols.

The IDCRP Regulatory Affairs staff, RCHSPB monitors, and USU ID IRB staff continue to work collaboratively to advance ethical, multicenter, militarily-relevant infectious disease research.





Education

The IDCRP remains committed to the development of clinical research skills in military medical officers across the spectrum of their professional development, beginning with assisting in the education of the newest medical student, to support for residents and fellows in graduate medical education and specialized MPH and PhD programs. During FY 2012 these activities have included the IDCRP's traditional role porting ID fellows and junior staff in National Capital Consortium (NCC) throughout the IDCRP network of military training facilities and the direction of graduate level courses at the Uniformed Services University. These courses rely upon the strong support of the IDCRP's professional staff with significant help from our NIAID partners.

In addition, a Clinical Research Workshop for fellows and junior staff was presented by IDCRP faculty during the 2012 Joint Military Infectious Disease Research Program (MIDRP), Armed Forces Infectious Disease Society (AFIDS), and IDCRP Annual Meeting, which was held in Rockville, MD. This year's meeting focused on blood-borne pathogens, particularly HIV and Hepatitis C. The fellows' workshop focused on a cross-section of research skills, and encouraged fellows and junior staff to explore their future options by reflecting on the rich career experiences shared by several senior leaders from our community.



Of note, the USU F. Edward Hébert School of Medicine Curriculum Reform Process moved from a planning stage to become operational, reorganizing the critical pre-clerkship work into an 18 month sequence of seven integrated clinical and basic science modules. This exciting new curriculum requires significant support from clinicians and scientists as a much greater emphasis is placed on high quality small group teaching experiences. The IDCRP staff has volunteered hundreds of hours to support the success of this new curriculum. This has included providing instruction in the fields of epidemiology, biostatistics, pathology, microbiology, infectious diseases, and basic clinical skills. Our staff has worked through several USU Departments, including Preventive Medicine and Biometrics, Internal Medicine, Pediatrics, Microbiology and Immunology, and Emerging Infectious Diseases. Despite the challenges of The Base Realignment and Closure (BRAC) Process, and increasing geographic diversity of our facilities, the IDCRP remains committed to the education and training of our military medical officers in clinical research.



Col (ret) Martin Ottolini
Director of the Education Program



Protocols by Focus Area

Trauma/Combat Related Infections

IDCRP#	Protocol Short Title	PI	IDCRP Sites	Status
IDCRP-024	Trauma Infectious Disease Outcomes Study (TIDOS)	Tribble	WRNMMC, SAMMC, LRMC	Active
IDCRP-044	Case Control Study of Osteomyelitis Risk Factors in Orthopedic Injury (OIF/OEF)	Tribble	WRNMMC, SAMMC, LRMC, USU	Active
IDCRP-072	<i>In vitro</i> activity of arbekacin against MDR bacteria	Zapor	WRNMMC, USAM-MDA	IRB

Acute Respiratory Infections

IDCRP#	Protocol Short Title	PI	IDCRP Sites	Status
IDCRP-045	ARIC: Acute Respiratory Infection Consortium	Arnold	NMCSD, SAMHS, WRNMMC, MAMC, NMCP	Active
IDCRP-045-01	Flu PRO	Arnold	NMCSD, SAMHS, WRNMMC, MAMC, NMCP, USU	Active
IDCRP-046	H1N1 Antibody Plasmapheresis	Danko	NMCSD, NMRC	Active
IDCRP-056	Prevnam vs Pneumovax to Boost Immunity in HIV (RV150)	Crum-Cianflone	NMCP, NMCSD, SAMMC, WRNMMC	F/U Complete
IDCRP-058	Retrospective H1N1 Case Review	Rajnik	NMCP, NMCSD, SAMMC, WRNMMC, MAMC, KAFB, USU	Analysis
IDCRP-059	Transmission of Seasonal Influenza in four Distinct Regions of Peru	Montgomery	NAMRU-3	Active
IDCRP-060	Acute Undifferentiated Febrile Illness in Cambodia	Yasuda	NAMRU-2 Cambodia	Active
IDCRP-061	Avian Influenza Transmission in Asia	Yasuda	NAMRU-2 Cambodia	Active
IDCRP-062	Anti-Influenza A H1N1 Immune Plasma for Treatment of Influenza A H1N1 2009	Danko	NMCP, NMCSD, NIAID, NMRC	Active
IDCRP-070	Self-Administered Nasal Influenza Vaccine (SNIF)	Burgess	NMCSD, SAMHS	Active
IDCRP-073	Adv3 seromarker prevalence and predictor	Voss	USU	Active

Operational Deployment/Travel Related Infections

IDCRP#	Protocol Short Title	PI	IDCRP Sites	Status
IDCRP-021	Latent TB Screening in the DoD	Mancuso	Ft. Jackson	Fully Enrolled
IDCRP-032	Leptospira Antibiotic Susceptibility	Maranich	SAMMC	Active
IDCRP-037	TravMil – Infections in DoD Travelers	Maguire	NMCP, NMCS, WRNMMC	Active
IDCRP-064	Comparison of Q Fever Serology Performed at 4 Reference Laboratories	Gutierrez	WRNMMC	Active
IDCRP-065	OCONUS Travelers' Diarrhea	Riddle	Camp Lemonnier - Djibouti, BATUK - Kenya, Camp Bastion - Afghanistan	Active

Biodefense/Emerging Infectious Diseases

IDCRP#	Protocol Short Title	PI	IDCRP Sites	Status
IDCRP-022	Ebola/Marburg Vaccine Phase II Study in Uganda	Ledgerwood	MUWRP, USMHRP, NIAID	Fully Enrolled
IDCRP-026	Pre-existing immunity, antigen expression, and vaccinia	Ngaay	WRAIR	Active
IDCRP-057	Detection and prevalence of <i>Rickettsia parkeri</i>	Myers	NMCP, NHJ	Active

Skin and Soft Tissue Infections

IDCRP#	Protocol Short Title	PI	IDCRP Sites	Status
IDCRP-001	MRSA Chlorhexidine RCT at MCB Quantico	Whitman	Marine Corps Base Quantico, WRNMMC, USU	Analysis
IDCRP-003	MRSA Skin Infections in HIV (RV210)	Weintrob/ Crum-Cianflone	NMCP, NMCS, WRNMMC, SAMMC	F/U Complete
IDCRP-035	Phase I/II <i>Staphylococcus aureus</i> Toxoids Vaccine Trial	Landrum	NMCP, SAMMC, USU	Analysis
IDCRP-055	Ft. Benning SSTI Prevention Strategies Study	Ellis	Ft. Benning, USU	Analysis
IDCRP-066	Cost Burden of MRSA-SSTI	Morrison	USU, APHC, NMCPHC	Active
IDCRP-068	Shipboard MRSA	Curry	NMCP, USU	Fully Enrolled
IDCRP-074	MRSA SSTI Epidemiology	Ellis	Ft. Benning, USU	Active

Human Immunodeficiency Virus (HIV)

IDCRP#	Protocol Short Title	PI	IDCRP Sites	Status
IDCRP-000	HIV Natural History Study (RV168)	Agan	NMCP, NMCSO, SAMMC, TAMC, WRNMMC	Enrolling
IDCRP-008	Observational Study of Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV	Shaffer/ Sawe/ Sereti/ Ananworanich	NIAID, USAMRU-K, KEMRI, Thai Red Cross AIDS Research Center	F/U Complete (Kenya) Enrolling (Thailand)
IDCRP-015	Atorvastatin effects on VL and Immune Activation in HIV	Ganesan	NMCSO, NNMC, NIAID	F/U Complete
IDCRP-016	Neurocognitive Impairment in HIV	Agan/Crum-Cianflone	NMCSO, SAMMC, WRNMMC	F/U Complete
IDCRP-023	MRSA Predisposition in HIV (MRSA 2)	Crum-Cianflone	NMCSO, WRNMMC	F/U Complete
IDCRP-038	Strategic Timing of AntiRetroviral Therapy (START)	Agan	NMCP, NMCSO, WRNMMC, SAMMC, USU	Enrolling
IDCRP-041	Phase I/II study of CD4-Zeta gene Modified T-cell administration	Aronson	WRNMMC	F/U Ongoing
IDCRP-053	H1N1 Vaccine Response in HIV vs Non-HIV	Crum-Cianflone	NMCP, NMCSO, SAMMC	F/U Complete
IDCRP-056	Pneumovax vs Prevnar to Boost Immunity in HIV (RV150)	Crum-Cianflone	NMCP, NMCSO, NNMC, SAMMC, WRAMC	F/U Complete
IDCRP-063	RCT of Rifaximin to mitigate chronic immune activation in HIV	Ganesan	WRNMMC, NIH CC, Univ of Pittsburgh	Pre-enrollment

Sexually Transmitted Infections

IDCRP#	Protocol Short Title	PI	IDCRP Sites	Status
IDCRP-067	Gonorrhea Resistance	Macalino	Ft. Bragg, Ft. Carson, Ft. Lewis, Ft. Sam Houston	Enrolling
IDCRP-069	STI Serosurvey	Agan	USU	Retrospective

Sub-Studies of IDCRP Protocols

IDCRP #	Sub-study Title	PI	IDCRP Sites	Project Status
IDCRP-000-xx	HIV Natural History Sub-studies (RV168)	Agan	NMCP, NMCSO, NMMC, SAMMC, TAMC, WRAMC	
ID-CRP-000-02	Immune Response and Host Genetics (former Central memory T-cells) (RV168B)	Ganesan	All IDCRP-000 Sites	Retrospective
ID-CRP-000-03	HAART Outcomes (formerly Modeling VL response to HAART) (RV168C)	Okulicz	All IDCRP-000 Sites	Retrospective
ID-CRP-000-05	HIV Controllers (RV168E)	Okulicz	All IDCRP-000 Sites	Retrospective
ID-CRP-000-08	African American setpoint viral load genome wide association study (RV168H)	Weintrob	All IDCRP-000 Sites	Retrospective
ID-CRP-000-17	Chronic Kidney Disease in HIV (RV168Q)	Ganesan	All IDCRP-000 Sites	Retrospective
ID-CRP-000-18	Pharmacogenomics of protease-inhibitor Response in HIV(RV168R)	Weintrob	All IDCRP-000 Sites	Retrospective
ID-CRP-000-20	Pneumonia in HIV (RV168T)	Johnson	All IDCRP-000 Sites	Retrospective
ID-CRP-000-22	Vitamin D, Testosterone, DEXA and Osteoporosis in HIV(RV168V)	Sherwood/ Aronson	WRNMMC	Retrospective
ID-CRP-000-23	HIV Extreme Phenotype Genetics (RV168W)	Michael/ Weintrob	All IDCRP-000 Sites	Retrospective
ID-CRP-000-24	HIV Care Cost Effectiveness Analysis	Agan	All IDCRP-000 Sites	Retrospective
ID-CRP-000-25	Hepatitis B vaccine Host Response and HIV Outcomes	Okulicz	All IDCRP-000 Sites	Retrospective
ID-CRP-000-26	Sexually Transmitted Infections (STI) in the HIV NHS	Macalino	All IDCRP-000 Sites	Retrospective
ID-CRP-000-32	Envelope glycoprotein phenotypes in HIV +	Quinnan	All IDCRP-000 Sites	Retrospective

Finances

IDCRP continues to develop new, modified or extended contracts, cooperative agreements and grants in order to successfully execute collaborative clinical research. Since FY2008, the Program has successfully leveraged core research funds from the NIAID to bring in other collaborations and funding sources. In FY 2012, IDCRP received \$31 million in multi-year funding. This represents a growth of 11% over 2011 (\$28M) and 72% over 2010 (\$18M). The largest ongoing protocols include the HIV Natural History Study, the Trauma Infectious Disease Outcomes Study (TIDOS), and the Acute Respiratory Infection Consortium (ARIC) Natural History Study.

The bar chart on page 45 shows how IDCRP funding has increased over time. The current year budget has grown from \$10.3M in FY 2009 to \$24.3M in FY 2013. The budget in FY 2013 is supported by current year funds and prior year multi-year funding sources that extend into FY 2013 and beyond. The amount of multi-year funding received each year includes “leveraged funds”, funding for “one year” projects from FY 2012 dollars, and funding for “multiyear” projects that are to be used over more than one year (ie: FY 2012, FY 2013 and FY 2014).

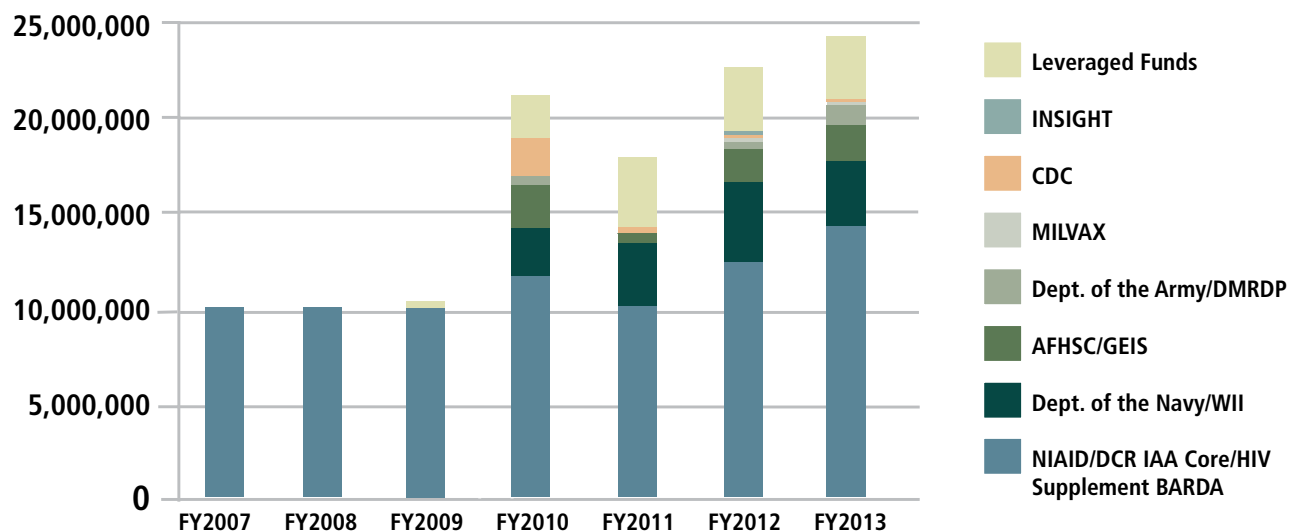
The majority of funding received in FY 2012 is primarily for use in FY 2013. IDCRP continues to be successful in leveraging the core support received from the NIAID and our core capabilities to obtain funding from other key stakeholders.



Gerard Adore
Chief, Operations and Finance



Joel Curtin
Deputy Chief, Operations and Finance



Major Funding Sources for IDCRP Research

Partners:

National Institute of Allergy and Infectious Diseases (NIAID) Interagency Agreement

Biomedical Advanced Research and Development Authority (BARDA)

Department of the Navy Bureau of Medicine and Surgery (BUMED), Wounded, Ill & Injured Program (WII)

Armed Forces Health Surveillance Center (AFHSC)/DoD Global Emerging Infectious Surveillance & Response System (GEIS)

Department of the Army (DoD-Deployment Related Medical Research Program) (DMRDP)

Military Vaccine Agency (MILVAX)

Centers for Disease Control and Prevention (CDC)

International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Publications and Presentations

Reverse chronological order:

1. Schlett CD, Grandits GA, Millar EV, Whitman TJ, Tribble DR. **Marine Recruit Adherence in a Skin and Soft Tissue Infection Prevention Trial: Implications for Recruit Research and Public Health Application.** Mil Med 2012 Nov; 177(11): 1335-1342.
2. Warkentien T, Rodriguez C, Lloyd B, Wells J, Weintrob A, Dunne JR, Ganesan A, Li P, Bradley W, Gaskins LJ, Seillier-Moiseiwitsch F, Murray CK, Millar EV, Keenan B, Paolino K, Hospenthal DR, and Tribble DR. **Invasive Fungal Infections following Combat-related Injuries.** Clin Infect Dis 2012; Oct 5 [Epub ahead of print].
3. Johnson MD, Schlett CD, Grandits GA, Mende K, Whitman TJ, Tribble DR, Hospenthal DR, Murray PR. **Chlorhexidine Does Not Select for Resistance in *Staphylococcus aureus* Isolates in a Community Setting.** Infect Control Hosp Epidemiol 2012 Oct;33(10):1061-3.
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6. Whitman TJ, Schlett CD, Grandits GA, Millar EV, Mende K, Hospenthal DR, Murray PR, Tribble DR. **Chlorhexidine gluconate reduces transmission of methicillin-resistant *Staphylococcus aureus* USA300 among marine recruits.** Infect Control Hosp Epidemiol 2012 Aug;33(8):809-16.
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10. Landrum ML, Neumann C, Cook C, Chukwuma U, Ellis MW, Hospenthal DR, Murray CK. **Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005-2010.** JAMA 2012 Jul 4;308(1):50-9.
11. Ganesan A, Fieberg A, Agan BK, Lalani T, Landrum ML, Wortmann G, Crum-Cianflone NF, Lifson AR, Macalino G; Infectious Disease Clinical Research Program HIV Working Group. **Results of a 25-Year longitudinal analysis of the serologic incidence of syphilis in a cohort of HIV-infected patients with unrestricted access to care.** Sex Transm Dis. 2012 Jun; 39(6):440-8. Epub 2012 Mar 15.
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Accepted Research Related Manuscripts

1. Crum-Cianflone N, et al. **Skin and soft tissue infections among HIV-infected person in the late HAART era.** Accepted Int J STD AIDS.
2. Ganesan A, et al. **The level of TCM in early HIV infection does not correlate with disease progression.** Accepted J Infect Dis.

Research Related Presentations

2012 Infectious Diseases Society of America Meeting, San Diego, CA

1. Mesner O, Bebu I, Landrum M, Macalino G, Agan BK, Chun HM. **CD4 reconstitution for HIV/HBV co-infected individuals on HAART.**
2. Ward-Demo P, Mesner O, Bebu I, Landrum M, Agan B, Crum-Cianflone N, Johnson E. **CD4 Nadir at HAART Initiation Is Not Associated with the Development of Community Acquired Pneumonia.**
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4. Minidis N, Singh M, Landrum M, Agan B, Okulicz J. **Improvement in Delayed-Type Hypersensitivity (DTH) Test Responsiveness During ART is Independent of Pre-ART CD4 Cell Count.**
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10. Arnold J, Fairchok M, Maguire J, Danaher P, Rajnik M, McDonough E, Blair P, Mor D, Ridore M, Ottolini M, Burgess T and Millar E. **Severe Influenza-like Illness Due to Human Rhinovirus Infection in a Military Beneficiary Population.**
11. Mende K, Beckius M, Zera W, Yu X, Cheadle K, Landrum M, Crawford K, Weintrob A, Tribble DR, Wortmann G, Lloyd B, Murray C and the IDCRP TIDOS Investigative Team. **Phenotypic and Genotypic Changes Over Time and Across Facilities of Serial Colonizing *Escherichia coli* Isolates Recovered from Injured Service Members.**

12. Schlett C, Lanier J, Wilkins K, Chu X, Law N, Smith T, Hadley A, McCrory O, Morrison S, Crawford K, Millar E, Gorwitz R, Tribble DR and Ellis M. ***Staphylococcus aureus* Nasal Colonization with First-episode *S. aureus* Skin Infection.**
13. Curry J, Lalani T, Wilkins K, Crawford K, Ellis M, Maguire J. **Prevalence of *Staphylococcus aureus* Colonization and Risk Factors for Infection among Naval Personnel in a Shipboard Setting.**
14. Gaskins L, Weintrob A, Li P, Bradley W, Lu D, Millar E, Crawford K, Lloyd B, Wortmann G, Murray C, Tribble DR and the IDCRP TIDOS Investigative Team. **Bacteriologic Profile of Colonization, Disease and Antimicrobial Resistance among Military Personnel with Combat-related Traumatic Injury.**

2012 International AIDS Conference, Washington, DC

1. Momanyi L, Ouedraogo L, Tian J, Agan B, Mican J, Ngeno H, Shikuku K, Sawe F, Shaffer D, Sereti I. **Incident tuberculosis after initiation of antiretroviral therapy in rural Kericho, Kenya**
2. Ngeno HC, Biomdo M, Tian J, Liu M, Kilel L, Kiptoo I, Agan B, Sawe F, Sereti I, Shaffer D. **Non-disclosure of HIV status among patients with advanced HIV starting antiretroviral therapy (ART) is associated with virologic failure: the Kericho IRIS Study**
3. Ngeno HC, Langat J, Tian J, Liu M, Biomdo M, Soy C, Agan B, Sawe F, Sereti I, Shaffer D. **Prevalent low body mass Index (BMI) among patients with advanced HIV initiating antiretroviral therapy (ART) and risks of subsequent hospitalization and mortality: the Kericho IRIS Study**
4. Narendran G, Andrade B, Nayak K, Sher A, Swaminathan S, Sereti I. **Higher plasma levels of IL-6 initiation of anti-retroviral therapy (ART) are associated with increased risk of paradoxical immune reconstitution inflammatory syndrome (IRIS) in patients with HIV and tuberculosis**

2012 International Workshop on HIV Observational Databases, Athens, Greece

1. Seillier-Moiseiwitsch F, Bebu I, Mesner O, Tate J, Macalino G, Rimland D, Weintrob A, Justice AC, Agan B; Infectious Disease Clinical Research Program HIV Working Group. **Recalibrating the VACS Index on the U.S. military HIV national history study cohort.**
2. Bebu I, Mesner O, Tate J, Macalino G, Rimland D, Weintrob A, Justice AC, Seillier-Moiseiwitsch F, Agan B; Infectious Disease Clinical Research Program HIV Working Group. **The VACS Index accurately discriminates risk of death and AIDS among U.S. military active duty and beneficiaries starting HAART, but requires calibration in this population.**

2012 Conference of Retroviruses and Opportunistic Infections, Seattle, WA

1. Landrum M, Agan B, Wortmann, Okulicz J, IDCRP HIV Working Group. **Delayed-Type Hypersensitivity and Hepatitis B Vaccine Responses, in vivo Markers of Cellular and Humoral Immune Function, and the Risk of AIDS or Death**
2. Landrum M, Okulicz J, Ganesan A, Wortmann G, Agan B. **Hepatitis B Virus Vaccine Response Is Inversely Related to the Duration of Untreated HIV Infection**
3. Moore D, Roediger M, Eberly L, Blackstone K, Hale B, Weintrob A, Ganesan A, Agan B, Letendre, Crum-Cianflone N. **Identification of an Abbreviated Test Battery for Detection of HIV-associated Neurocognitive Impairment in an Early-Treated HIV-infected Cohort**
4. Crum-Cianflone NF, Moore D, Letendre S, Poehlman-Roediger M, Eberly L, Ganesan A, Weintrob A, Jonson E, Agan B, Hale B. **An Early Diagnosed and Treated HIV Cohort Shows Low Rates of Neurocognitive Impairment**
5. Guest J, Weintrob A, Rimland D, Rentsch C, Bradley W, Agan B, Marconi V. **A Comparison of HAART Outcomes: US Military HIV Natural History Study vs. HIV Atlanta Veterans Affairs Cohort Study**
6. Krishnan S, Rono E, Tian J, Shikuku K, Agan B, Ngeno H, Kirui F, Khamadi S, Sawe F, Sereti I. **Characteristics of Immunologic Non-responders in an ARV-Naive, Advanced HIV Cohort in Kenya**
7. Mahnke Y, Greenwald J, DerSimonian R, Roby G, Antonelli L, Sher A, Roederer M, Sereti I. **HIV-1+ Patients with IRIS Exhibit a Selective Expansion of Polyfunctional Pathogen-specific CD4+ T Cells**
8. Sandler N, Crum-Cianflone N, Weintrob A, Roque A, Egan K, Marquart L, Tieu, Beu I, Estes J, Douek D. **Decreased MRSA-Specific CD4+ T cell Responses May Explain Predisposition to MRSA Skin and Soft Tissue Infections among HIV+ Persons**

Extremity War Injuries VII - A Decade at War: Evolution of Orthopaedic Combat Casualty Care, Washington, D.C.

1. Murray CK. **Combating Battlefield Gram-Negative Infections.**
2. Tribble DR. **Invasive Fungal Wound Infections: Emerging Combat Threat.**

International Conference on Emerging Infectious Diseases, Atlanta, GA

Arnold J, Maguire J, Lalani T, Sutter D, Fairchok M, Rajnik M, Weintrob A, Landrum M, Echols S, McDonough E, Blair P, Defang G, Vancea A, Seillier-Moiseiwitsch F, Ridore M, Ottolini M, Burgess T, Kortepeter M and Millar E. **Geographic Variability in the Etiology of Influenza-like Illness (ILI).**

Annual Meeting of the Surgical Infection Society, Dallas, TX

Malone D, Rodriguez C, Dunne J, Wells J, Fleming M, Warkentien T, Weintrob A, and Tribble DR. **Trials and tribulations; the expedited development of an IFI CPG.**

Advanced Technology Applications for Combat Casualty Care, Ft. Lauderdale, FL

Weisbrod A, Dunne JR, Rodriguez C, Weintrob A, Seillier-Moiseiwitsch F, Malone D, Lloyd B, Warkentien T, Wells J, Murray CK, Li P, Bradley W, Gaskins LJ, Shah J, and Tribble DR. **Fungus Among Us: A large Case Series of Invasive Fungal Infections in Combat Casualties.**

Annual Meeting of the American Association for the Surgery of Trauma, Kauai, HI

Rodriguez C, Weintrob A, Dunne JR, Seillier-Moiseiwitsch F, Malone D, Weisbrod A, Lloyd B, Warkentien T, Wells J, Murray CK, Li P, Bradley W, Gaskins LJ, Shah J, Tribble DR, and the IDCRP TIDOS Group. **Clinical Significance of Mold Culture Positivity in Combat Trauma.**

Investigator Additional Professional Activities

Administrative Duties:

Consultant for Biodefense to the Army Surgeon General

Army OTSG representative to the Able Response Biodefense exercise, Seoul, Korea

Research Specialty Leader for the Navy Surgeon General

Invited Lectures and Panels:

Grand Rounds, USU PMB Department

Grand Rounds, San Antonio Military Medical Center Department of Pediatrics

Lecturer for joint NIAID, FDA, DTRA, BARDA meeting on animal model development for Biothreat Agents

Participant, NIAID meeting assessing post-exposure prophylaxis for BSL-4 laboratory occupational exposures

Guest Editors:

Special Issue of the *Journal of Sexually Transmitted Diseases*

Reviewers:

Antiviral Research, Biosecurity and Bioterrorism, Clinical Infectious Diseases, Emerging Health Threats Journal, Infectious Diseases in Clinical Practice, Journal of Infectious Diseases, Journal of Pediatrics, Military Medicine, Pediatric Infectious Disease Journal, Pediatrics, PLoS Neglected Tropical Diseases, PLoS One, Statistics in Medicine, Vaccine

Peer Review Panel Members for the following:

CDC Peer Review Panels for Extramural Clinical Research

Influenza Pathogenesis and Therapy

Annual meeting program committee, American Society of Tropical Medicine and Hygiene

IIPT Oversight Committee, Military Infectious Disease Research Program

JPC-2 Proposal Review Committee, Military Infectious Disease Research Program

Scientific Advisory Board Member, Pattern Of Non-Communicable Diseases In People Living With HIV/AIDS [PaNDA]

Clinical Activities:

Attending physician, Inpatient Infectious Disease Consult Service and Internal Medicine Service
Outpatient Attending Physician Infectious Disease Clinic

Educational Activities:

PhD dissertation committee members
Chair of the Pre-Clerkship Curriculum Committee and Council of Module Directors
Steering Committee for Curriculum Reform, USU
USU faculty committee (e.g., Spaced Education)

Course Directors for the following USU courses:

PMO514 – Epidemiology and Control of Infectious Diseases
PMO900 – Introduction to Clinical Research
PMO996 – Clinical Trial Design & Analysis

Course Instructors for the following:

Introduction to Clinical Trials
Fundamentals of Epidemiology & Biostatistics
Preventive Medicine small group sessions on diagnostics and study design
Georgetown Biostatistics course
USAMRIID's Medical Management of Biological Casualties Course
Military Tropical Medicine
Introduction to Clinical Medicine II and III



IDCRP at a Glance

What we are: The IDCRP was established as an ongoing collaboration between the National Institute of Allergy and Infectious Diseases (NIAID) and the Uniformed Services University (USU) to foster partnerships on clinical infectious disease research that are relevant to the military and the NIAID.

Who we are: Program Director: Mark G. Kortepeter, MD, MPH, FACP
Colonel, us Army Medical Corps

Where we are: The Program Coordination Center at USU in Bethesda, Maryland .
IDCRP research personnel are at 10 military medical treatment facilities: WRNMMC, NMCP, NMCS, SAMMC, MAMC, TAMC, Martin ACH (Ft. Benning), LRMC, Womack AMC (Ft. Bragg) 12 other collaborating military research sites: NHRC, WRAIR, NMRC, USAMRIID, MUWRP, KEMRI, NAMRU-6, NAMRU-2, USAISR, Camp Lemonnier, Camp Bastion, Evans ACH (Fort Carson)

Number of currently active protocols: 40

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Rockville, MD 20852

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Mission: To conduct infectious disease clinical research of importance to the military through a unique, adaptive, and collaborative network to inform health policy and practice and disseminate findings in peer reviewed literature.

Vision: To substantially reduce the impact of infectious diseases in the military population through collaborative clinical research.